Proposal about "Microneedles For Drug Delivery: Achieving consistent and controlled drug release in coated Microneedles"

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Motivation

Drug-coated microneedles are an important transdermal drug delivery device that combines the precision of microfabrication with the simplicity of patch administration. This technique has received much attention because of its potential to change therapeutic delivery, especially in chronic pain management, where existing methods frequently fail to maintain regular drug levels [6]. The capacity to carefully construct these microscale devices with controlled drug coatings provides unprecedented prospects for providing focused, painless drug administration without the limitations of traditional needles or oral drugs [11].

Despite these promising characteristics, coated microneedles present a significant challenge in clinical use: variable and poorly regulated drug release patterns. Existing coating technologies often yield inconsistent drug loading, uneven distribution across the needle surface, and erratic release behavior [2]. The shortcomings manifest as therapeutic uncertainty, where patients receive inconsistent doses that jeopardize the efficacy and safety of treatment. These limitations hinder the clinical translation of microneedle technology, especially in therapeutic applications where treatment efficacy directly correlates with the dose delivered [9].

The purpose of our research

This research aims to create novel strategies for obtaining consistent drug coatings and regulated release profiles in microneedle devices to solve these pressing issues. To systematically optimize coating techniques and formulation parameters towards developing standardized procedures that ensure reproducible and uniform drug delivery and bridge the gap between the promise of microneedle technology and practical clinical delivery. The physical coating and the chemical formulation components will be optimized as part of the project and validated through intensive in-vitro and in-vivo testing. Finally, this work seeks to marry the theoretical promise of microneedle technology with its real-world clinical implementation [12].

Technical Gaps, Challenges, and Limitations of Current Methods

Main Limitation

Our primary concern in the proposal is the uneven release of drug control. The primary challenge with the current microneedle technique is achieving constant and controlled drug release characteristics. Drug delivery rates in current systems are variable, influencing treatment efficacy and patient outcomes. It is challenging to maintain constant therapeutic doses because of this major constraint, which allows unexpected drug concentrations to reach the target area. Achieving consistent drug delivery is significantly hampered by the complex interplay of coating techniques, material characteristics, and release mechanisms, especially in applications that call for exact dosage control [19].

Coating Distribution Challenges

Uneven drug distribution during the coating process provides a severe technological challenge in creating microneedles. Current coating techniques usually lead to uneven coating thickness throughout the microneedle surface and varying drug loading between needles. This unequal distribution directly impacts the dependability of medication delivery and makes it challenging to guarantee constant therapeutic dosages. Problems further compromise delivery performance with coating stability and adherence during storage and application settings beyond simple coating variability [2].

Release Profile Optimization Barriers

A key barrier to the development of coated microneedle technology is still the control of drug release kinetics. Unpredictable release patterns are frequently seen in current formulations, typified by an undesirable initial burst release followed by irregular delivery rates. The technology's use in treatments requiring exact dose regimens is limited by the absence of trustworthy techniques to alter these release characteristics [17].

Manufacturing Scale-up Limitations

Maintaining constant coating quality and performance becomes extremely difficult when laboratory-scale research gives way to industrial manufacturing. Current production techniques need help with larger-scale quality control and batch-to-batch repeatability. The lack of standardized production procedures and the difficulty of concurrently managing many coating characteristics create significant obstacles to commercial application. These scalability issues must be resolved before using coated microneedle technology in clinical settings [19].

Innovation

The proposed study is innovative because it focuses on issues like uneven coating and erratic drug release rates to improve the efficacy of microneedles for drug delivery. Moreover, present limitations could be resolved through this research and a more accurate, efficient drug delivery system could be developed by improving the various creative parameters, like exploring the coating techniques that can result in uniform coating of particles and a better understanding of drug-polymer ratio effects on drug release kinetics.

Research Aim 1: Investigation and Comparison of Microneedle Coating Methods for Sustained Drug Delivery

The Goal of the Research

Our proposal focuses on systematically comparing the following four microneedle coating methods (dip coating, inkjet coating, immersion coating, and drop coating) to find the best method to obtain a controlled and continued administration of insulin [4]. We will analyze and compare coating uniformity (target: <±10% variation), drug loading efficiency (target: >85%), and release kinetics (target: <30% release in first hour, sustained release over 48 hours) across these approaches to determine the most successful and scalable methodology for pharmaceutical coating applications. This proposal aims to compare different techniques of coated Microneedles to check which is the best technique. We will choose the best method based on Coat uniformity, Drug Loading, and Release Profile.

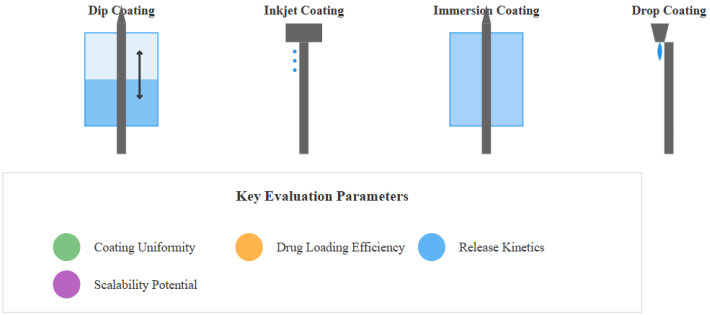


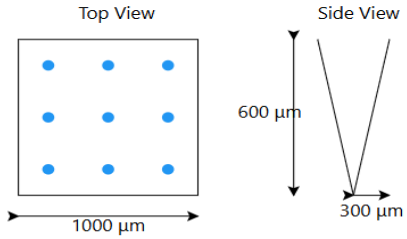
Figure #1 :*Systematic Comparison of Microneedle Coating Methods*

Hypothesis

We hypothesize that different coating methods yield significantly different drug release profiles and coating uniformities. Specifically, dip coating is expected to provide more controlled and sustained drug release (20-30% release in the first hour, followed by consistent release of 1-2% per hour for 48 hours) due to its ability to create uniform, shaft-specific coatings (thickness variation <±10%). Conversely, predicts increased variability with other methods (>±20% thickness variation) and unpredictable patterns of release (>50% release within 2 h). We hypothesize that when vapor deposition and dip coating are involved in developing drug-eluting coatings; the nature of the process is controlled in comparison to vapor deposition which can be inconsistent in terms of coating and drug release properties based on studies conducted [3].

Experimental Design

Our experimental design implements a systematic approach to developing and characterizing coated microneedles for controlled insulin delivery. The PLGA-based microneedles were formed using 3D-printed PDMS molds with fixed dimensions (height = 600 µm, base = 300 µm) for constant needle geometry [6]. To achieve accurate measurement of drug distribution, insulin will be labeled with



Figure#2: *Microneedle Array Structure that we want to design.*

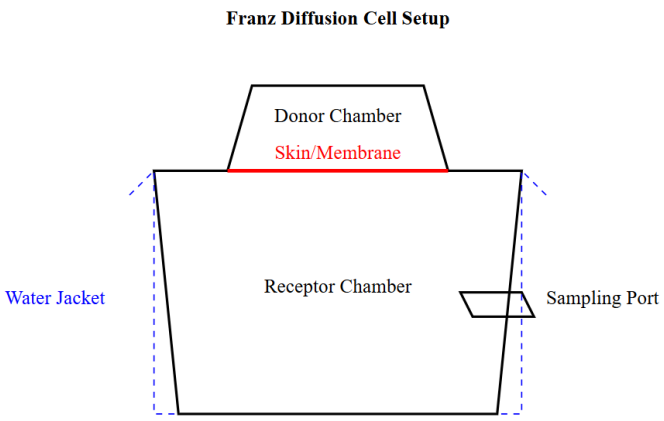
Rhodamine for quantitative evaluation of the coating uniformity and release mechanism. Four different coating methods will be compared in controlled environmental conditions (T: 22±2°C; RH: 45±5%), involving intense optimization and standardization for each technique. Characterization of the performance is performed with SEM imaging for a morphology study, an HPLC analysis for drug loading measurement, and an in-depth kinetics study of the release using Franz diffusion cells with pig skin models [21]. This comprehensive approach provides a complete picture of the capabilities and limitations of all coating technologies.

Methodology

In this Aim, we describe a systematic three-phase methodology for developing and characterizing coated microneedles for insulin delivery as a proof of concept. Step 1: Material Case Preparation: Poly(lactic-co-glycolic acid) (PLGA), the most widely used bio-polymer, was selected as the primary polymer matrix due to its biocompatibility and controlled degradation properties [13]. Our microneedles are produced using 3D-printed PDMS molds, allowing for repeatable and reproducible needle geometry. Insulin is tagged with Rhodamine fluorescent dye for drug distribution tracking with extensive dialysis purification of the protein to remove unreacted dye molecules. Conjugation is validated by UV spectroscopy to confirm that we have conjugated a dye and measure the labeling efficiency [13].

The coating process uses four different methods in a strictly controlled environment. In the dip coating process, control of microneedle shaft dip depth and speed of immersion (2 mm/s insertion speed and 5-second dwell time) allows selective coating of the microneedles with the drug-polymer formulation [21]. To uniformly coat the microneedles, inkjet coating involves piezo-driven nozzles (30 µm diameter) to deposit controlled droplets (20 pL) directly on the microneedle surface [21]. For immersion coating, the coating solution was based on GA (40 mg per 10 mL) submerging the whole array and was withdrawn from the solution at a controlled rate of 0.5 mm/s for 30 s; for drop coating, the same solution based on GA was calculated similarly and directly transferred by a single droplet (2 µL) onto the array to be distributed by gravity [5].

To ensure an accurate characterization, multiple analytical techniques are employed. Coating morphology and thickness uniformity (10 points/needle) are evaluated by SEM imaging [7]. The coating dissolved and analyzed by a validated HPLC method quantifies drug loading efficiency [16]. The release kinetics and penetration efficacy are examined in Franz diffusion cells using



Figure#3: *Franz Diffusion Cell Setup for Aim 1*

PBS (pH 7.4) as the release medium and porcine skin as the diffusion barrier [14]. Samples are taken at intervals of 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours and drug release is measured using fluorescence spectrometry [20].

Expected Results

We systematically evaluated the different methods down to the expected results of microneedle coating methods, and are selecting a dip method that is expected to be the most efficient for controlled delivery of insulin. We expect the dip coat to allow for better performance by yielding microneedles with highly uniform coatings focused specifically on the needle shaft rather than diffusing to the base [4]. In this regard, this approach is predicted to provide the least variation in coating distribution, within a variation of ±10% [2]. One of the key advantages expected from dip coating is that it provides a regulated and prolonged release profile throughout 24-48 h which is essential for maintaining the normal physiological levels of insulin. However, for comparison, other methods of inkjet, immersion, or drop coating are unlikely to exhibit the same limitations.

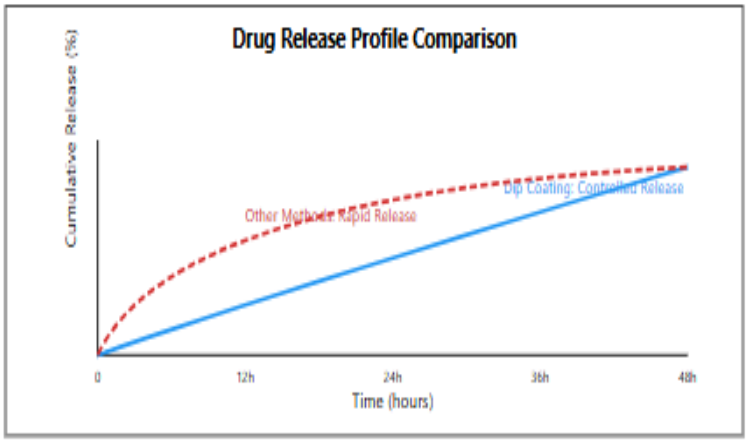


Figure # 4: *Dip coating demonstrated the most slowest, most controlled release rates over 24-48 hours due to consistent coating thickness*

While inkjet coating might offer good precision, we predict it will demonstrate moderate variation in coating uniformity (15-20%) with faster release kinetics [21]. Despite potentially achieving high initial drug loading, immersion coating is expected to suffer from variable surface coverage, leading to inconsistent release patterns [7]. Drop coating is anticipated to show the least favorable outcomes with poor uniformity and rapid, irregular release profiles [20]. The results of these comparisons will provide a solid basis for further studies aimed at advancing microneedle technology and creating more effective insulin delivery systems. Dip coating is probably the best way to provide sustained and continuous

Parameters	Dip Coating	Inkjet Coating	Immersion Coating	Drop Coating
Coating uniformly	Excellent ,Even coating,Variation < 10%	Good ,Precise deposition,Variation 15–20%	Variable, Full surface coating,Variation > 25%	Poor,Uneven distribution, Variation > 30%
Drug Loading	Sustained release	Rapid release	Inconsistent release	Rapid, irregular release
Release Profile	24–48 hours	12–24 hours	6–18 hours	4–12 hours

Figure # 5: *Results of Comparing different techniques of Coating Microneedles based on Coating uniformity, Drug Loading, and Release Profile.*

insulin release, which is necessary for efficient therapeutic use, according to this thorough analysis.

Research Aim 2: Optimizing the Insulin-to-Polymer Ratio in Microneedle Dip Coatings

Hypothesis

Based on our building upon the findings from Aim 1, we hypothesized that the insulin-to-PLGA ratio plays a crucial role in determining drug loading efficiency and release kinetics of drug coated onto microneedles. Higher polymer content should help facilitate the sustained release characteristic of these yeast cells while higher insulin content could potentially yield an increased burst release [15]. An ideal drug-to-carrier ratio would strike the necessary compromise between drug loading capacity and controlled release behavior required for successful therapeutic action.

Goal of experiment

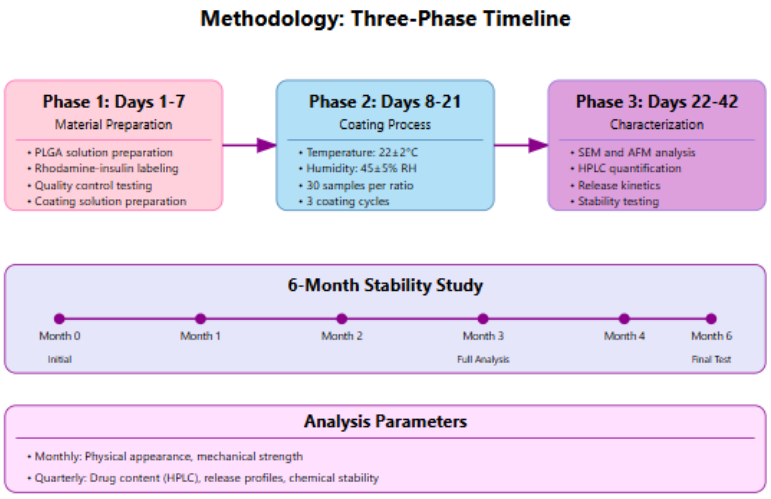
Our experiment goal is to attempt to find a suitable ratio of insulin and PLGA polymer in microneedle coatings to obtain a sustained release for 24–48 h. This optimization will be based on the successful dip-coating method established in Aim 1 and serve as the precursor for the validation studies in Aim 3, paving the way for a robust and reproducible insulin delivery system engineered via coated microneedles.

Experimental Design:

In our study, six specific insulin-to-PLGA ratios of insulin and PLGA obtained from the literature are evaluated systematically, these are, 1:1, 1:2, 1:3, 1:4, 2:1, and 3:1. In all cases, coating solutions contain 5% w/v solid content in ethanol, trehalose (0.5% w/v) to stabilize the coating materials [21]. First, insulin is labeled with Rhodamine fluorescent dye to enable precise tracking of the distribution and release of insulin and the free dye molecules are subsequently removed through dialysis to purify the products. UV spectroscopy is then used, to confirm dye conjugation and to determine labeling efficiency [7]. A detailed characterization of every ratio is performed, including SEM images (500x, 1000x, and 2500x magnification), AFM PD testing, and testing at 5 points along the length of the needle to determine coating thickness. The drug loading is determined using validated HPLC analysis (UV detector at 214 nm; the standard curve is established in the range of 0.1–100 μg/mL at least six times per formulation) [14]. To study the release kinetics, Franz diffusion cells were employed using a porcine skin model and samples were taken at appropriate intervals (0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours) at controlled temperatures (32±0.5 °C) condition [20].

Methodology

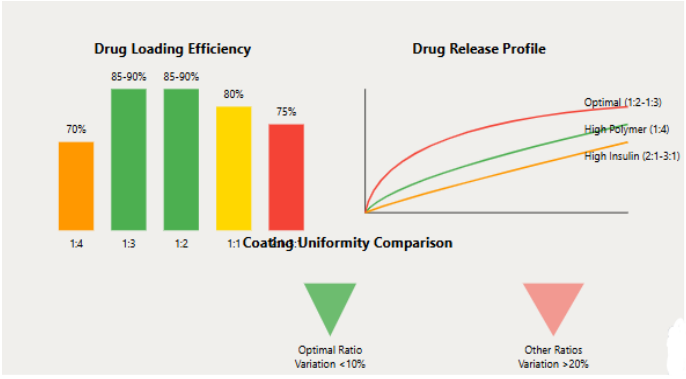
A structured three-phase framework is followed as our methodology in order to maximize the analysis of each insulin-to-PLGA ratio. The first phase, which is from Days 1-7 of the process, includes preparation of PLGA solutions in ethanol with varying concentrations, confirmation of Rhodamine-insulin labeling, quality control of each formulated solution, and preparation of coating solutions with six different ratios. The coating process (Days 8-21) involves an optimized dip-coating process set-up with temperature and humidity control (22±2°C, 45±5% RH) enabling the production of 30 samples per ratio with three coating cycles done at 30 seconds between each cycle. Full characterization (Days 22-42) consists of additional morphological studies using SEM and AFM, HPLC for drug loading measurement, and Franz diffusion cells for studying the release kinetics. In addition, a six-month stability study performed in parallel observed the physical aspect of the samples as well as the content of the drug and release profiles. This includes the use of a texture analyzer to assess the mechanical strength as well as the stability of the chemical content through HPLC, in order to ensure that the improved formulation is site stable [3].



Figure#6 : *The Three -Phase Timeline Methodology for Aim 2*

Expected Results

Through our developed systematic assessment, we expect drug loading efficiency of between 85 and 90 percent with variations of under ten percent to be achieved using insulin to PLGA ratios of between 1:2 and 1:3 as the most ideal formulations. These ratios should be able to achieve ideal release profiles, with the first hour of use only having a burst release of less than 30 percent and sustaining release at 1 to 2 percent every hour for up to 48 hours [3]. Coating characterization is also anticipated to demonstrate controlled biopolymer morphology, where the variation in coating thickness does not exceed ten percent, allowing reproducible skin penetration. Stability studies need to be carried out to show that the insulin potency and structural integrity of the

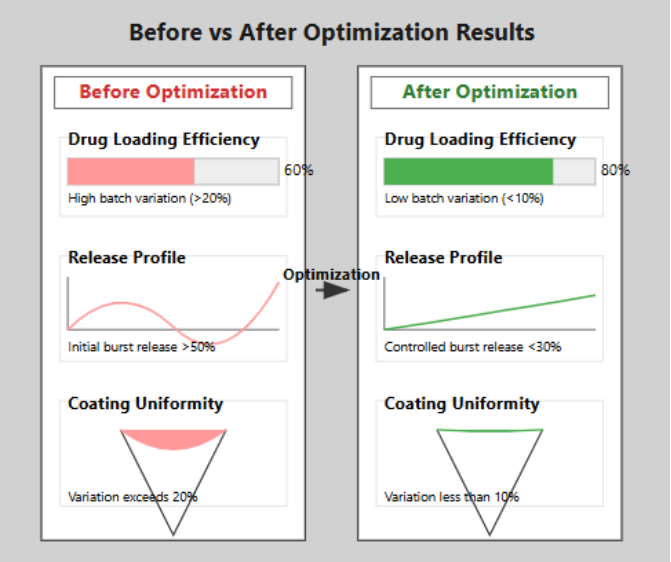


Figure#7: *Insulin -to-PLGA ratios Performance*

coating shall be retained for at least three months when stored at 4 degrees. C. Formulation with higher polymer ratios such as 1:4 would only be able to achieve lower drug loading efficiencies of less than 70 percent but would be able to sustain release more. Formulations with insulin ratios of 2:1 or 3:1 have higher chances of releasing over 50 percent of the content within the first hour and sustaining the therapeutic effectiveness [9].

This optimization can be appreciated better when comparing pre and post-optimization performance. The earliest formulations had maximum drug loading efficiencies of only about sixty percent with variability of over twenty percent from batch to batch indicating good reproducibility of the process.

Following optimization, we markedly improved to 80% drug loading efficiency with batch variation reduced to less than 10%, ensuring more consistent and efficient drug delivery potential. The release profile also improved significantly, moving from a problematic first burst release of more than 50% of the drug content to a more controlled release profile with less than 30% initial burst followed by a steady release. This step leads to the full therapeutic dose of insulin while preventing life-threatening rises in blood glucose[17]. The coating uniformity data validates that we have achieved our optimization goals both qualitatively and quantitatively, as evidenced by the thickness variation being reduced from greater than 20% to less than 10% Complete optimizations are required for patient safety with safe-onset-of-action controlled drug release, treatment efficacy with reproducible drug loading & release patterns, manufacturing robustness with reduced batch-to-batch variation, cost-effectiveness with reduced insulin waste and regulatory approval through better uniformity and consistency [5]. The result will be a well-characterized and reproducible formulation which will serve as a basis for validation studies in Aim 3 and ultimately, an optimal insulin delivery system.



Figure# 8: Designed Picture To see *Comparison of Before vs After Optimization*

Research Aim 3: Validate Optimized Dip-coated Microneedle Coatings Through In-vitro and In-vivo Testing Using Insulin as a Model Drug

Goal of the experiment

Our goal in this experiment is to assess the effectiveness and safety of Dip -coated insulin Microneedles with the view to transforming Insulin Delivery through the mouth model. Based on the optimization outcomes of Aims 1 and 2, the roles have a link with substantial insulin microneedles drug incorporation. The intensive in-vitro and in-vivo testing will determine

whether the system can achieve insulin release that lasts for a long period, manage the glucose level efficiently, and approve the compatibility of the system with the body tissue. The positive outcome of this study will pave the way for Clinical application as well as other advantages more than available conventional insulin delivery methods.

Hypothesis

We propose the delivery of microneedles that have been dip-coated with insulin to improve the microneedle/skin penetration and should theoretically show favorable results to subcutaneous injection delivery methods. Method: Using an optimized polymer formulation, the dip-coating process will lead to in vitro uniform and sustained insulin release profiles, as well as in vivo glucose regulation and minimal tissue disruption. This novel drug delivery strategy is likely to improve patient compliance with low administration frequency and high biocompatibility.

Experimental Design:

Here, we utilize a systematic two-stage validation plan that encompasses both in-vitro and in-vivo studies. Strat-M synthetic membranes are employed on Franz diffusion cells to quantitatively determine the insulin release kinetics and compare coating uniformity in the in-vitro phase [1]. Such a controlled environment allows accurate assessments of the performance and reliability of our dip-coating technology. The in-vivo phase uses a widely accepted rat model, which contains three groups (n=6/group): dip-coated insulin microneedles (the test group), subcutaneous insulin injections (positive control) and uncoated microneedles (negative control). This comprehensive design allows for a direct comparison of our technology against current standard treatments while assessing safety and efficacy parameters [8].

Methodology:

In-vitro Testing: In-vitro assessment: Strat-M membranes are mounted on Franz diffusion cells where phosphate-buffered saline (PBS, pH 7.4) is used as the receptor medium [14]. Stable dip-coated microneedle patches using our optimized coating formulation that contains 1 IU of Insulin will be applied using a spring-loaded applicator to ensure consistent penetration depth. At pre-specified time points (0.5, 1, 3, 6, 12, 24, and 48 hrs) [1], we will collect receptor medium samples which will be subjected to ELISA to quantify the kinetics of insulin release[2]. To assess the reproducibility of the manufacturing process, multiple batches will be tested with the statistical data analyzed by coefficient of variation and ANOVA. The microneedles will be examined after the application to study the integrity of the coating and the dissolution shape.

In-vivo Testing: Male Sprague-Dawley rats (250-300g) will be randomly assigned to groups (n=6 in each group) of three experimental groups [9]. After a 12 hr fast (free access to water), blood glucose readings will be taken from the tail vein. In the test group, dip-coated insulin microneedle patches (1 IU insulin/patch) will be administered to shaven dorsal skin with a standardized spring-loaded applicator. Our positive control will be individual per conventional subcutaneous injections of insulin (1 IU) and our negative control will be uncoated microneedles [8] . Blood will be drawn at correspondingly matched times (0.5, 1, 3, 6, 12, 24, and 48 h) for simultaneous assessment of blood glucose (glucometer) and plasma insulin (ELISA) [9]. Skin biopsies will be obtained 24 and 48 hours after application for histological assessment of local tissue response and any potential inflammatory responses.

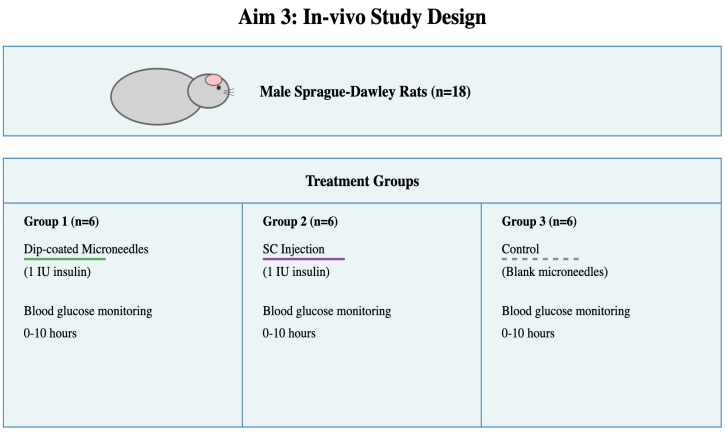


Figure # 9: *In-vivo setup with 18 rats divided into three groups: dip-coated microneedles (1 IU insulin), subcutaneous injection (1 IU insulin), and a control with blank microneedles. Blood glucose was monitored for 10 hours.*

Expected Results :

For in-vitro studies, we expect to see release profiles of controlled insulin release over 24-48 hours with an initial burst release followed by a sustained level of delivery. This prediction is due to the optimized dip-coating process which formed uniform and stable insulin layers with controllable dissolution characteristics[2]. We anticipate the batch-to-batch variation to be < 10% (std dev), which is consistent with the precision of our dip-coating methodology and our stringent quality control parameters. The figure shows that insulin is delivered from the microneedles throughout 48 hours. Initially, insulin is released quickly, allowing for an instant impact. Then, the discharge is continuous and regulated, lasting a long period [22]. The modest error bars indicate that the results remain consistent between batches. This demonstrates that microneedles may administer insulin reliably and in a regulated manner, resolving the issue of inconsistent release.

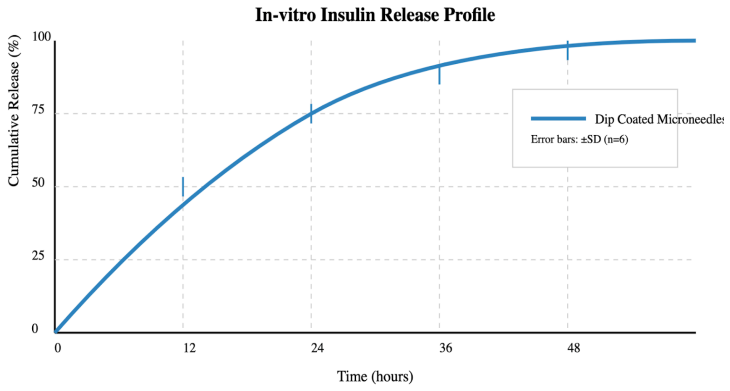


Figure #10 : *In-vitro release profile of insulin from dip-coated microneedles over 48 hours,showing sustained release pattern with initial burst release followed by controlled release (n=6, mean ±SD)*

Based on the above in-vivo studies, we anticipate that these dip-coated microneedles will provide similar or better glucose control (blood glucose ≤120 mg/dL) as compared to

subcutaneous injections of insulin administered over 6-8 h [3]. We expect to see slow increases in plasma insulin concentrations that then maintain those therapeutic levels, as is shown to correlate with our in-vitro release profiles. Histology data should detect little to no tissue disruption and inflammatory response confirming that our dip-coated microneedle system shows biocompatibility [12]. These expectations are based on initial studies, together with systematic optimizations of our dip-coating formulation and process variables [14]. As illustrated in the figure, dip-coated microneedles (green line) reduced blood glucose rapidly and kept it in healthy ranges longer than subcutaneous injections (purple line). The control group (gray line) didn't show any changes. This suggests that microneedles have better glucose control.

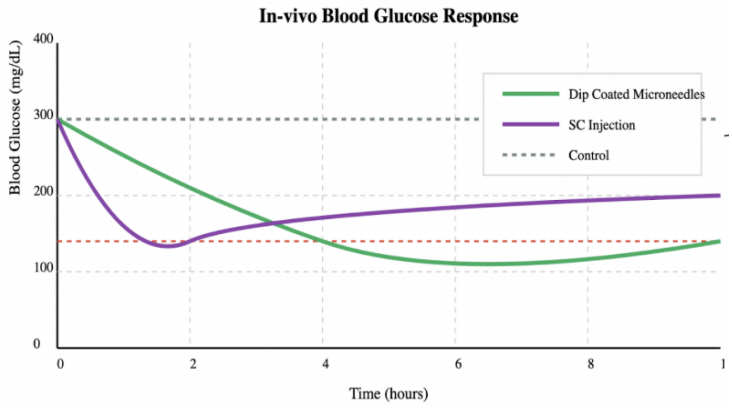
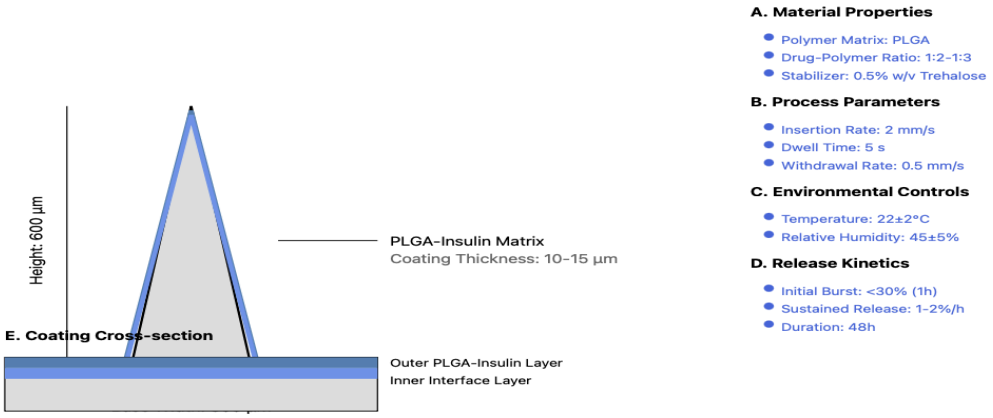


Figure # 11: *Blood glucose levels in diabetic rats following administration of insulin via dip-coated microneedles,subcutaneous injection, or control treatment. Target glucose level (250-300g) shown by red dashed line (n=6 per group)*

Microneedle Final Coating Design



Figure#12: *Microneedle Final Coating Design*

According to our proposal, our microneedle coating design utilizing a finely engineered PLGA-based microneedle array with a matrix iridescence represents a major innovation and technological advancement within the field of drug delivery. Uniform geometry was achieved via 3D-printed PDMS molds of 600 μm height and 300 μm base width of the 10x10 array [6]. The most significant advancement is its improved dip-coating process that yields reproducible drug-PLGA films in defined conditions (22±2°C, 45±5% RH) [2,21].

The exact parameters of this coating process—a two mm/s insertion speed, a 5-second rest period, and a 0.5 mm/s withdrawal rate—create a coating that is 10–15 μm thick and varies by less than ±10% [2]. The formulation includes a 5% w/v ethanol solution suspended in 0.5% w/v trehalose as a stabilizing excipient and an optimum drug-to-PLGA ratio of 1:2 to 1:3 [17, 21].

This meticulously constructed system achieves more than 85% drug loading efficiency. It has a regulated release profile, with less than 30% initial burst release in the first hour followed by a steady release of 1-2% every hour for 48 hours [2]. Our Coating microneedle efficiency is confirmed by extensive in-vitro testing utilizing Franz diffusion cells with Strat-M membranes and in-vivo experiments in Sprague-Dawley rats, which monitor medication concentrations and tissue reactions [9]. Morphology, drug content analysis, and surface roughness studies were done using SEM, HPLC, and AFM as quality control procedures, and stability over 6 months at 4 degrees Celsius was also assessed [14].

There are many advantages of this modern delivery method for therapeutic use. While the adaptable platform was initially tried with insulin, it can be adapted for other therapeutic agents, and its less invasive delivery relative to standard injections enhances patient compliance [18]. Batch-to-batch relative standard deviation is maintained below 10%, and the controlled release profile ensures optimal drug delivery kinetics for sustained therapeutic action [2]. The system has mechanical reliability with a force greater than 0.1 N per needle, assuring the successful penetration of the skin [3]. Its 4°C long-term stability test further confirms the potential of practical storage [21]. Additionally, high loading efficiency leads to less waste of medication and comprehensive characterization methods ensure drug release behavior reliability [2]. Due to the ease, speed, and scalability of our process (using 3D printed molds), our coating microneedle can serve as an alternative to the traditional drug delivery methods for therapeutic applications requiring controlled release [6].

Conclusion

The proposed study would use a systematic three-phase approach to create an optimal microneedle coating technology for insulin administration. These assumptions imply that for more uniform coating (<±10%) and more controlled release profiles, a ratio of insulin to PLGA (poly lactic-co-glycolic acid) between 1:2 and 1:3 would be advantageous in this process via dip coating [17, 2, 21]. However, these are theoretical predictions that have not been subjected to empirical tests. This would require the type of comprehensive testing, both in-vitro and in-vivo, and data that the suggested complete testing methodology would deliver, to validate these theories and give realistic performance measurements. Future efforts may move this coating technique to additional therapeutic drugs, explore additional polymer matrices, and develop automated processes for scale-up.

It will be essential to follow in future research the impact that layer count and choice of polymer might have on drug release [1]. Effects of such polymers in the long term, which might include their breakdown and accumulation in tissues, should be used to assess the safety of this approach. To assess the practical potential of the system for diabetes treatment, further stability studies and clinical trials will be necessary. As this is a study proposal, all targeted outcomes and corresponding performance measures must be validated in experiments before making any conclusions about the success of the initiative.

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Note: All the figures were designed based on our proposal by us.