

**MODELLING POLYMERIC MICRONEEDLE
BASED TRANSDERMAL DRUG
DELIVERY SYSTEMS**

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**DEPARTMENT OF CHEMICAL ENGINEERING
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DELIVERY SYSTEMS**

by

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DEPARTMENT OF CHEMICAL ENGINEERING

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Certificate

This is to certify that the thesis entitled “**Modelling Polymeric Microneedle Based Transdermal Drug Delivery Systems**” submitted by **Mr. Prateek Ranjan Yadav** to the Indian Institute of Technology Delhi, for the award of the degree of Doctor of Philosophy, is a record of the original bonafide research work carried out by him. He has worked under our supervision and has fulfilled the requirements, which to our knowledge, has reached the requisite standard for the submission of this thesis. The results contained in this thesis have not been submitted in part or full to any University or Institute for the award of any degree or diploma.



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Abstract

Polymeric microneedles (MN) based transdermal drug delivery (TDD) has received significant interest due to their potential for painless administration, non-invasiveness, and ability to deliver a wide range of drugs. After its placement inside the skin, the interstitial skin fluid (ISF) enters MN, and the drug transports into the skin. The sustained release of the drug is the primary objective of this kind of drug delivery method. Based on the physical nature of the polymer used, the polymeric MN is divided into dissolving microneedles (DMN) and swelling microneedles (SMN). DMN absorbs the skin water and completely dissolves in the skin, which results in the release of drugs from the needle into the skin. The SMN tends to attach to the MN base throughout the delivery process and come out intact from the skin without polymer dissolution in the skin. SMN is further divided into phase-transition microneedles (PTMN) and hydrogel-forming microneedles (HFMN), with the former having drug loaded in the MN domain like DMN and the latter having drug loaded in the reservoir attached at the base in the form of a lyophilised tablet. The type of MN and polymer used in their fabrication is chosen based on the required drug delivery rate in the skin. Various parameters that control the drug delivery are MN physicochemical parameters (e.g., dimension, shape, composition), skin properties, and drug pharmacokinetics in blood. It is difficult to optimise all the parameters experimentally. For polymeric MNs to become a frontrunner in delivering drugs in the foreseeable future, the development of mathematical models that accurately represent the system is vital. Researchers have developed models taking into consideration the effect of geometric and design parameters for different types of MNs.

Here, we have developed a generalised mathematical model for SMN and DMN, incorporating the key parameters defining the skin properties and physicochemical properties of the MNs,

such as the polymer swelling capacity, mechanical deformation, and amount of drug loading. Drug solubilisation and binding within the drug vehicle and skin and its effect on the bioavailability of the drug are studied, which were not considered in earlier models developed for polymeric MNs. The developed model outlines the required steps and data needed to estimate the performance of polymeric MNs, which are envisaged to help design improved experiments for the design of polymeric MNs. Some practical scenarios are also simulated to demonstrate the applicability of the developed framework. The coupled diffusion-reaction-deformation model is simulated using COMSOL Multiphysics[®], a finite element commercial software.

For swelling PTMN, the model is simulated for insulin loaded in polyvinyl alcohol MN. The contact mechanics at MN and skin interface is introduced to account for the resistive force exerted by the deformed skin to MN swelling in the case of SMN. It was observed that skin viscoelasticity affects drug transport by resisting swelling and pushing part of MN outside the skin. The model was able to predict the final insulin concentration in blood and was shown to be in good agreement with the reported experimental data of *in vivo* insulin diffusion study performed on Bama pig.

The model was further extended for the swelling HFMN and validated with *in vitro* diffusion studies of ibuprofen sodium (IBU) across excised porcine skin, showing that around 20% of the loaded IBU in lyophilised wafer was delivered in 24 hours. It was observed that increasing IBU solubility in the reservoir can achieve high drug transport across the skin. Results showed that although diffusion is cited as the dominant release mechanism, drug dissolution and binding also play a major role in regulating the overall drug delivery profile.

In addition, a modelling framework was developed for DMN made up of hyaluronic acid and model drug insulin. For 0.44 IU of insulin loading in the DMN, the proposed mathematical model predicts that insulin diffuses into the blood to reach a maximum concentration of 151 $\mu\text{IU ml}^{-1}$ in 1 hour and that 95% of insulin is removed from the blood within 5 hours. The developed model was able to predict the final drug release profile and was shown to be in good agreement with the *in vivo* and *in vitro* reported experimental data.

The generalised modelling framework developed in the thesis can be used with any form of polymeric MN, regardless of shape, composition, and drug loading. The proposed modelling strategies will be helpful for pharmaceutical and biotechnological industries as well as professionals working in the field of regulatory affairs focusing on polymeric MN-based TDD systems.

Keywords: Finite element modelling, Hygroscopy, Mathematical modelling, Polymeric microneedle, Transdermal drug delivery

सार

पॉलीमरिक माइक्रोनीडल्स (MN) आधारित ट्रांसडर्मल ड्रग डिलीवरी (TDD) को दर्द रहित प्रशासन, गैरआक्रामकता और दवाओं की एक विस्तृत श्रृंखला देने की क्षमता के कारण महत्वपूर्ण रुचि मिली है। त्वचा के अंदर प्रविष्टि के बाद, अंतरालीय त्वचा द्रव (ISF) MN में प्रवेश करता है और त्वचा में दवा परिवहन होता है। दवा की निरंतर रिहाई इस तरह की दवा वितरण विधि का प्राथमिक उद्देश्य है। उपयोग किए गए बहुलक की भौतिक प्रकृति के आधार पर, पॉलीमरिक MN को घुलने वाले माइक्रोनीडल्स (DMN) और सूजन माइक्रोनीडल्स (SMN) में विभाजित किया जाता है। DMN त्वचा के पानी को अवशोषित करता है और त्वचा में पूरी तरह से घुल जाता है, जिसके परिणामस्वरूप सुई से त्वचा में दवाओं की रिहाई होती है। SMN प्रसव प्रक्रिया के दौरान MN आधार से लगा रहता है और त्वचा में पॉलीमर विघटन के बिना त्वचा से बरकरार रहता है। SMN को आगे चरण-संक्रमण माइक्रोनीडल्स (PTMN) और हाइड्रोजेल बनाने वाले माइक्रोनीडल्स (HFMN) में विभाजित किया गया है, जिसमें पहले में DMN जैसे MN डोमेन में दवा भरण की जाती है और बाद में लियोफिलाइज्ड टैबलेट के रूप में बेस पर जुड़े जलाशय में दवा भरी होती है। उनके निर्माण में उपयोग किए जाने वाले MN और पॉलीमर के प्रकार को त्वचा में आवश्यक दवा वितरण दर के आधार पर चुना जाता है। दवा वितरण को नियंत्रित करने वाले विभिन्न मापदण्ड MN भौतिक रासायनिक मापदण्ड (जैसे, आयाम, आकार, संरचना), त्वचा के गुण और रक्त में दवा फार्माकोकाइनेटिक्स हैं। प्रयोगात्मक रूप से सभी मापदण्डों को अनुकूलित करना मुश्किल है। निकट भविष्य में दवाओं को वितरित करने में अग्रणी बनने के लिए पॉलिमरिक एमएन के लिए, गणितीय मॉडल का विकास जो सिस्टम का सटीक प्रतिनिधित्व करता है, महत्वपूर्ण है। शोधकर्ताओं ने विभिन्न प्रकार के MN के लिए ज्यामितीय और डिजाइन मापदण्डों के प्रभाव को ध्यान में रखते हुए मॉडल विकसित किए हैं।

यहां, हमने SMN और DMN के लिए एक सामान्यीकृत गणितीय मॉडल विकसित किया है, जिसमें MN के त्वचा गुणों और भौतिक रासायनिक गुणों को परिभाषित करने वाले प्रमुख मापदण्डों को शामिल किया गया है, जैसे बहुलक सूजन क्षमता, यांत्रिक विरूपण, और दवा भरण की मात्रा। दवा वाहन और त्वचा के भीतर दवा घुलनशीलता और बंधन और दवा की जैव उपलब्धता पर इसके प्रभाव का अध्ययन किया जाता है, जिसे पॉलीमरिक MN के लिए विकसित पहले के मॉडल में नहीं माना जाता था। विकसित मॉडल पॉलिमरिक MN के प्रदर्शन का अनुमान लगाने के लिए आवश्यक चरणों और डेटा को रेखांकित करता है, जो पॉलीमरिक MN के डिजाइन के लिए बेहतर प्रयोगों को डिजाइन करने में मदद करने के लिए परिकल्पित हैं। विकसित ढांचे की प्रयोज्यता को प्रदर्शित करने के लिए कुछ व्यावहारिक परिदृश्य भी अनुकरण किए जाते हैं।

युग्मित प्रसार-प्रतिक्रिया-विरूपण मॉडल को COMSOL मल्टीफिजिक्स[®], एक परिमित तत्व वाणिज्यिक सॉफ्टवेयर का उपयोग करके अनुकरण किया गया था।

सूजन PTMN के लिए, मॉडल को पॉलीविनाइल अल्कोहल MN में भरण किए गए इंसुलिन के लिए अनुकरण किया जाता है। MN और त्वचा इंटरफ़ेस पर संपर्क यांत्रिकी को SMN के मामले में MN सूजन के लिए विकृत त्वचा द्वारा लगाए गए प्रतिरोधक बल के लिए पेश किया गया है। यह देखा गया कि त्वचा की चिपचिपाहट सूजन का विरोध करके और त्वचा के बाहर MN के हिस्से को धक्का देकर दवा परिवहन को प्रभावित करती है। मॉडल रक्त में अंतिम इंसुलिन एकाग्रता की भविष्यवाणी करने में सक्षम था और बामा सुअर पर किए गए विवो इंसुलिन प्रसार अध्ययन के रिपोर्ट किए गए प्रयोगात्मक डेटा के साथ अच्छे समझौते में दिखाया गया था ।

मॉडल को सूजन HFMN के लिए आगे बढ़ाया गया था और उत्पादित पोर्सिन त्वचा में इबुप्रोफेन सोडियम (आईबीयू) के इन विट्रो प्रसार अध्ययनों के साथ मान्य किया गया था, जिसमें दिखाया गया था कि लियोफिलाइज्ड वेफर में लोड किए गए आईबीयू का लगभग २०% २४ घंटे में वितरित किया गया था। यह देखा गया कि जलाशय में आईबीयू घुलनशीलता बढ़ने से त्वचा में उच्च दवा परिवहन प्राप्त हो सकता है। परिणाम बताते हैं कि हालांकि प्रसार को प्रमुख रिलीज तंत्र के रूप में उद्धृत किया जाता है, दवा विघटन और बाध्यकारी भी समग्र दवा वितरण प्रोफाइल को विनियमित करने में एक प्रमुख भूमिका निभाते हैं।

इसके अलावा, DMN के लिए एक मॉडलिंग ढांचा विकसित किया गया था जो हाइलूरोनिक एसिड और मॉडल दवा इंसुलिन से बना था। DMN में इंसुलिन लोडिंग के ०.४४ आईयू के लिए, प्रस्तावित गणितीय मॉडल भविष्यवाणी करता है कि इंसुलिन १ घंटे में $1.51 \mu\text{IU ml}^{-1}$ की अधिकतम एकाग्रता तक पहुंचने के लिए रक्त में फैलता है और ५ घंटे के भीतर रक्त से ९५% इंसुलिन हटा दिया जाता है। विकसित मॉडल अंतिम दवा रिलीज प्रोफाइल की भविष्यवाणी करने में सक्षम था और इन विवो और इन विट्रो रिपोर्ट किए गए प्रयोगात्मक डेटा के साथ अच्छे समझौते में दिखाया गया था।

शोध प्रबन्ध में विकसित सामान्यीकृत मॉडलिंग ढांचे का उपयोग आकार, संरचना और दवा भरण की परवाह किए बिना, पॉलिमरिक MN के किसी भी रूप के साथ किया जा सकता है। प्रस्तावित मॉडलिंग रणनीतियां फार्मास्यूटिकल और बायोटेक्नोलॉजिकल उद्योगों के साथ-साथ पॉलिमरिक MN-आधारित TDD प्रणाली पर ध्यान केंद्रित करने वाले नियामक मामलों के क्षेत्र में काम करने वाले पेशेवरों के लिए सहायक होंगी।

Table of Contents

Certificate.....	i
Acknowledgements.....	ii
Abstract.....	iv
Table of Contents.....	ix
List of Figures.....	xvi
List of Tables.....	xxi
List of Abbreviations.....	xxii
List of Variables.....	xxiv
1. Chapter 1.....	1
1.1 What are microneedles?.....	2
1.1.1 Polymeric microneedle.....	3
1.1.1.1 Types of polymeric MNs.....	5
1.2 Status of polymeric MNs: Opportunities and challenges.....	5
1.3 Scope and objectives of the thesis.....	8
1.4 Organization of thesis.....	9
2. Chapter 2.....	11
2.1 Mechanism and structure of different MNs.....	11
2.1.1 Solid MNs.....	11
2.1.2 Coated MNs.....	12
2.1.3 Hollow MNs.....	14
2.1.4 Dissolving MNs.....	14
2.1.5 Swellable MNs.....	15

Table of Contents

2.2	Importance of polymers as a material choice for MNs	16
2.2.1	Biocompatibility of polymer.....	17
2.2.2	Mechanical properties of polymer	18
2.3	Key human diseases studied by polymeric MNs.....	19
2.3.1	Diabetes	20
2.3.2	HIV and vaccination (Immunobiological administration).....	22
2.3.3	Contraception – Transdermal patches	22
2.3.4	Cancer	23
2.4	Kinetics of drug transport through polymeric MNs.....	26
2.4.1	Kinetics of drug transport through swellable polymers	27
2.4.1.1	Movement of molecules through swellable polymer network.....	28
2.4.1.2	Hydrodynamic theory	29
2.4.1.3	Obstruction theory.....	30
2.4.1.4	Free volume theory	32
2.4.2	Polymer drug interaction.....	33
2.5	Kinetics of polymer dissolution and drug release.....	34
2.6	Skin	35
2.6.1	Drug transport in skin	36
2.6.2	Mechanical properties of skin	37
2.7	Modelling MN-based drug delivery systems	40
2.7.1	Parameters for MN modelling.....	40
2.7.2	Modelling MN based drug delivery systems.....	42
2.8	Numerical techniques used in simulation.....	45

Table of Contents

2.9	Conclusions	46
3.	Chapter 3.....	48
3.1	Introduction	48
3.1.1	COMSOL Multiphysics® software	49
3.2	Numerical implementation.....	50
3.2.1	Setup for COMSOL Multiphysics®	51
3.3	Hygroscopic swelling material model	52
3.4	Solid mechanics	53
3.5	Contact mechanics	53
3.6	Moving boundary	54
3.7	Equation-based modelling to incorporate drug pharmacokinetic	55
4.	Chapter 4.....	57
4.1	Introduction	57
4.2	Mathematical model development	59
4.2.1	Governing equation	61
4.2.1.1	Mass transport equation	61
4.2.1.2	Mechanical properties of skin	63
4.2.2	Governing equation for drug pharmacokinetics	64
4.3	Input parameters	66
4.3.1	Diffusion coefficient.....	66
4.3.1.1	Diffusion coefficient within SMN	66
4.3.1.2	Diffusion coefficient in skin sublayers	68
4.3.2	Coefficient of hygroscopic swelling	69
4.4	Model geometry	70
4.5	Initial and boundary conditions	72

Table of Contents

4.6	Numerical implementation.....	74
4.7	Results and discussion.....	76
4.7.1	Species transport in MN.....	76
4.7.2	Effect of swelling and skin viscoelasticity.....	83
4.7.3	Effect of the amount of insulin loading	86
4.7.4	SMN penetration depth analysis.....	88
4.8	Conclusions	91
5	Chapter 5.....	93
5.1	Introduction	94
5.2	Materials and methods	97
5.2.1	Chemicals	97
5.2.2	Fabrication and characterization of hydrogel-forming MN.....	97
5.2.3	Preparation of IBU loaded reservoir	99
5.2.4	<i>In vitro</i> permeation study of ibuprofen sodium	100
5.3	Model development and parameters.....	101
5.3.1	Governing equation	102
5.3.1.1	Mass transport equation	102
5.3.1.2	Mechanical properties of skin	106
5.4	Input parameters	107
5.4.1	Diffusion coefficient inside MN.....	108
5.4.2	Diffusion coefficient in reservoir and skin	110
5.4.3	Drug binding and solubilisation rate constants.....	110
5.5	Initial and boundary conditions	111

Table of Contents

5.6	Model geometry and numerical implementation.....	114
5.7	Results and discussion.....	115
5.7.1	Fabrication and characteristics of microarray patches.....	115
5.7.2	Swelling kinetics of super swelling HFMN	118
5.7.3	<i>In vitro</i> permeation of ibuprofen sodium.....	123
5.7.4	Effects of reservoir properties on drug delivery profile.....	127
5.8	Sensitivity analysis	130
5.9	Conclusions	131
6.	Chapter 6.....	133
6.1	Introduction	134
6.2	Mathematical model development	135
6.2.1.1	Mass transport equation	136
6.2.1.2	Contact modelling between MN and skin layers	137
6.2.1.3	Governing equations for drug pharmacokinetics	138
6.3	Input parameters	139
6.3.1	Diffusion coefficient within MN and skin	140
6.3.2	Coefficient of hygroscopic swelling (β_h).....	140
6.3.3	Drug binding rate constants	141
6.4	Initial and boundary conditions	141
6.5	Numerical implementation.....	143
6.6	Results and discussion.....	145
6.6.1	Species transport and mechanical changes in MN	145
6.6.2	Effect of skin viscoelasticity on MN swelling and insulin release	152
6.7	Sensitivity analysis	155

Table of Contents

6.8	Conclusions	157
7.	Chapter 7.....	158
7.1	Introduction	158
7.2	Model development	161
7.2.1	Transport equation	163
7.3	Governing equation for insulin pharmacokinetic	165
7.4	Input parameters	166
7.4.1	Diffusion coefficient of insulin in MN.....	166
7.4.2	Diffusion coefficient in skin:	166
7.4.3	Drug binding and solubilisation rate constant	167
7.5	Initial and boundary conditions:	167
7.6	Numerical implementation.....	169
7.7	Results and discussion:.....	170
7.7.1	Concentration distribution profiles.	171
7.7.2	Effects of drug solubilisation rate inside MN on drug delivery profile.....	176
7.8	Conclusions	179
8	Chapter 8.....	180
8.1	Summary	180
8.1.1	Development of modelling framework for swellable MNs.....	180
8.1.2	Studying the effect of drug binding and retention using swelling hydrogel-forming MNs as a study case and comparison with <i>in vitro</i> experimental data.....	181
8.1.3	Coupled diffusion-binding-deformation modelling for phase-transition MNs-based drug delivery	181

Table of Contents

8.1.4	Modelling dissolving MN based drug delivery	182
8.1.5	Effect of skin type used in modelling MN based drug delivery	182
8.1.6	Comparing rates of drug transport from different types of polymeric MNs. .	184
8.2	Future scope.....	185
References:	188

List of Figures

Figure 1.1 Schematic of drug transport in MN treated skin. Drug transport is divided into four different stages.....	3
Figure 1.2. Bar charts displaying the total number of publications on MNs, and the number of MN publications related to polymeric MNs over the 5-year intervals. Information was accessed on 26/06/2021 at <i>www.scopus.com</i>	4
Figure 2.1 Schematic of different types of microneedles. (a) Solid, (b) Hollow, (c) Coated, (d) Dissolving, (e) Phase-transition, and (3) Hydrogel-forming MNs.	13
Figure 2.2 Schematic showing bounded and unbounded drugs in a swelled polymer matrix.	33
Figure 2.3 The swelling/dissolving polymer model is depicted schematically. L is the film thickness. The thickness of the glassy front is denoted by R. S denotes the swelling front's thickness (Kelly et al., 2019).....	35
Figure 2.4 Schematic of the human skin with thickness of various layers.	36
Figure 2.5 MN insertion profiling in skin layers. Force versus displacement data from a typical MN insertion profile (a) was evaluated for stiffness (b), force of insertion (c), and displacement at insertion (d) parameters for human and porcine skin before and after freezing at $-80\text{ }^{\circ}\text{C}$ for 48 hours (four human and four porcine subjects were tested at 35% and 100% RH; n = 8 per subject).Figure adapter with permission from (Ranamukhaarachchi et al. (2016).	39
Figure 2.6 Parameters affecting polymeric MN based TDD.	41
Figure 2.7 Relationship between sumatriptan released and time by the model (solid line) and <i>in vitro</i> (solid dots) for dissolving MN formulations performed by Ronnander et al., (2020). Reproduced with permission from the publisher.....	44
Figure 3.1 Flow diagram of modelling strategy used for predicting drug release.	49
Figure 3.2 COMSOL [®] standard workflow for creating a new model.	52
Figure 4.1 Mechanism of SMNs-based drug delivery, (a) Drug inside the reservoir (no diffusion), (b) Water entering into the MN causing swelling (still no drug diffusion), and (c) As the water reaches the reservoir base, drug diffusion triggers.	59
Figure 4.2 Schematic of a quarter of SMN inserted into the skin with initial and boundary conditions of the developed numerical model.....	74

Figure 4.3 Maximum insulin concentration in blood for varying maximum element size and (b) Semi log plot of maximum insulin concentration in blood for varying relative tolerance. The black arrow shows chosen mesh size and relative tolerance for our simulations, and (c) COMSOL mesh containing 26056 elements. Triangular meshing is done at MN/skin interface layer and MN-reservoir boundary layer for better accuracy. Tetrahedral meshing is done in the remaining boundaries and domain. 75

Figure 4.4 Streamline plot showing water flux and concentration distribution within SMN at different times due to imbibition of water into the SMN. (a) No water inside SMN at time $t = 0$, (b) water enters SMN causing swelling, (c) and (d) have similar flux and water distribution profiles, showing that the SMN is saturated with water in 15 minutes for the properties used in this work. 77

Figure 4.5 Change in physical properties of SMN after water absorption. (a) Mass change of MN and (b) Change in elastic modulus of MN. 79

Figure 4.6 Streamline plot showing flux and insulin concentration distribution at different time levels as the MN swells. (a) Reservoir loaded with lyophilised insulin, (b) almost 60% of insulin is released from the reservoir in 2 hours, (c) 90% insulin is released within 5 hours, and (d) almost all insulin is released from reservoir and SMN. 80

Figure 4.7 Time evolution of insulin properties in MN and blood. (a) Insulin effective diffusion coefficient (minor Y-axis) with an increase in water weight fraction within SMN major Y-axis), (b) Insulin concentration in blood from a SMNs patch containing 100 MNs, and (c) Pharmacokinetics of insulin in blood corresponding to various terms of equation 4.6. 82

Figure 4.8 (a) Changes in water weight fraction with a change in the hygroscopic swelling coefficient and (b) Change in insulin concentration in blood with the hygroscopic swelling coefficient. 85

Figure 4.9 Effect of insulin concentration in the reservoir on the drug dynamics in the blood. (a) Insulin concentration in blood, and (b) Rate of change of insulin concentration. 87

Figure 4.10 Effect of insertion depth (the gap between the skin and MN base) on the drug dynamics in the blood. (a) Insulin concentration in blood, and (b) Rate of change of insulin concentration. The inset figure shows the insertion depth of MN. 89

Figure 4.11 Mass conservation study of insulin. The horizontal red line shows that the total mass of insulin remains constant at any particular time for the modelling domain, which provides the confidence that the numerical simulations ensure mass conservation is consistent with what is expected in reality. 90

Figure 5.1 Mechanism of drug delivery using hydrogel-forming MNs. (a) Drug reservoir in the form of lyophilised tablet attached to MN base during the skin insertion; (b) MN swelling and drug release; (c) Intact MN patch removal from the skin without polymer residual in the skin. 95

Figure 5.2 Schematic representation of various experimental activities using super swelling MN. (a) MN preparation procedure; (b) Texture analyzer setup for carrying out the mechanical characterisation of prepared HFMN; (c) The Franz diffusion cell setup for *in vitro* permeation of ibuprofen sodium using HFMN. 100

Figure 5.3 2-D schematic of super swelling MN inserted into the skin with dimensions, initial and boundary conditions of the developed numerical model. 112

Figure 5.4 Meshing of super swelling MN and skin assembly containing 20450 domain elements, 3978 boundary elements, and 454 edge elements using COMSOL..... 115

Figure 5.5 Characterisation of prepared super swelling HFMN. (a) Digital image of MN array patch (19×19); (b) Light microscope image confirming the heights (600 μm) of MNs; (c) Line graph showing the percentage of holes created in Parafilm® M layers after manually inserting hydrogel-forming MN arrays (mean ± SD, n = 5); (d) Optical coherence tomography image of MN inserted into the porcine skin..... 117

Figure 5.6 Time evolution of measurable swelling parameters of MN in PBS (pH 7.4). (a) Percentage mass increase of MN array (mean ± SD, n = 5); (b) Digital image of swelled MN array patch. 119

Figure 5.7 Estimation of hygroscopic swelling parameter, β_h from the measured swelling data obtained using Franz diffusion cell. (a) Time evolution of percentage mass increase of MN array and comparison with the simulation output using $\beta_h = 2.05 \times 10^{-4} \text{ m}^3 \text{ kg}^{-1}$ (means ± SD, n = 5); (b) Time evolution of percentage volume increase of MN array and comparison with the simulation output using $\beta_h = 2.05 \times 10^{-4} \text{ m}^3 \text{ kg}^{-1}$ (mean ± SD, n = 5); (c) Variation of hygroscopic swelling strain with moisture concentration. The slope of the plot gives $\beta_h = 2.05 \times 10^{-4} \text{ m}^3 \text{ kg}^{-1}$ 122

Figure 5.8 Streamline plot showing flux and IBU concentration distribution at different periods (0, 2, 5, and 24 h) as the MN swells. These results have been obtained using the numerical mesh, as shown in Figure 5.5. 124

Figure 5.9 Variation in the amount of IBU present in different domains with time. (a) Plot comparing IBU permeation across excised porcine skin (measured acceptor compartment of Franz cells) and predicted permeation profile (mean ± SD, n = 5); (b) Retained IBU in a different domain ($k_R = 6 \times 10^{-9} \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$; $k_{MN} = 1 \times 10^{-4} \text{ s}^{-1}$; $k_{skin} = 1 \times 10^{-3} \text{ s}^{-1}$)..... 125

Figure 5.10 Comparison of the variation of IBU fluxes at different interfaces with time obtained from simulation ($k_R = 6 \times 10^{-9} \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$; $k_{MN} = 1 \times 10^{-4} \text{ s}^{-1}$; $k_{skin} = 1 \times 10^{-3} \text{ s}^{-1}$)..... 127

Figure 5.11 Effect of reservoir properties on the time evolution of IBU flux at MN/reservoir interface. (a) IBU diffusion coefficient ($D_{D,R}$) at a fixed solubilisation rate constant $k_R = 6 \times 10^{-9} \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (b) drug IBU solubilisation rate constant at a fixed $D_{D,R} (1 \times 10^{-11} \text{ m}^2 \text{ s}^{-1})$ 129

Figure 5.12 Sensitivity analysis of different parameters used in the simulation..... 130

Figure 6.1 Mechanism of drug transport from phase-transition MNs. (a) Drug loaded MN inserted into the skin, (b) MN swells by imbibing skin water leading to opening of polymer matrix and drug transport into systemic circulation, and (c) MN coming out from the skin intact..... 136

Figure 6.2 Schematic showing one-fourth part of phase-transition MN inserted into the skin with model's initial and boundary conditions..... 143

Figure 6.3 Mesh convergence study on COMSOL model. (a) Semi log plot showing effect of varying relative tolerance values on maximum insulin concentration obtained in blood, (b) Plot showing effect of varying maximum element size on maximum insulin concentration in blood, and (c) COMSOL mesh of PTMN and skin assembly containing 120367 elements based on chosen mesh size and relative tolerance values indicated by a black arrow. 144

Figure 6.4 Streamline plot showing water flux and concentration distribution within PTMN at different times (0, 0.5, 2, and 8 hours)..... 146

Figure 6.5 Change in physical properties of phase-transition MN with time due to skin water imbibition and its effect of insulin diffusivity. (a) Mass change of MN, (b) Elastic modulus change of MN, and (c) Insulin effective diffusivity (minor Y-axis). 147

Figure 6.6 Arrow plots show magnitude of contact pressure between MN and skin interface at different times (0, 0.5, 2, 8 hrs). 149

Figure 6.7 Cumulative drug release from MN and comparison with the experiments performed by Yang et al. (2012). 150

Figure 6.8 Insulin concentration in blood obtained through simulation on PTMN patch containing 135 MNs and its comparison with the experiments performed by Yang et al. (2015). Dotted line at the assumed C_{mt} to indicate the duration of the drug above the C_{mt} is denoted by T_i 152

Figure 6.9 Insulin release from phase transition MN at different hygroscopic swelling coefficient value of MN polymer. (a) Cumulative release of insulin in acceptor cell & (b) Insulin concentration in blood ($k_{MN} = 1.0 \times 10^{-4} \text{ s}^{-1}$ $k_{skin} = 1.0 \times 10^{-3} \text{ s}^{-1}$). 153

Figure 6.10 Magnitude of Maximum contact pressure experienced by the skin on different amounts of swelling of MN (major Y-axis) and part of MN outside the skin (minor Y-axis) when MN is fully saturated with water from skin..... 154

Figure 6.11 Sensitivity analysis of different parameters plotted against (a) Maximum concentration of insulin in blood (C_{max}) and (b) Time for which minimum concentration of insulin in blood is 1 ng ml^{-1} (T_i)..... 156

Figure 7.1 Schematic showing mechanism of drug transport from dissolving MN. (a) MN loaded with drug inserted into the skin, (b) ISF imbibition from the skin dissolves MN, and (c) Base of the MN is removed once MN is fully dissolved in the skin. 163

Figure 7.2 Meshing of dissolving MN and skin assembly containing 16437 elements. Fine meshing is done at MN/skin interface..... 170

Figure 7.3 ISF weight fraction in dissolving MN at a different time intervals (0,1, 30, and 60 minutes). Figure 7.2 shows the numerical mesh used to obtain these results. 172

Figure 7.4 Polymer weight fraction inside MN at a different time (0, 5, 30, and 120 minutes). 173

Figure 7.5 Plot comparing simulation results with experimental data obtained from Liu et al. (2012) for height change of MN. The value of ISF diffusion coefficient inside MN was estimated based on the height change data which gives the value of $D_{w,MN} = 5 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$. ($k_{MN} = 1 \times 10^{-6} \text{ m}^3 \text{ mol}^{-1} \text{ s}$). 174

Figure 7.6 Insulin concentration profiles in dissolving MN and skin at different times. (a) No insulin transport at $t = 0$, (b) & (c) Dissolution of the polymer occurs with insulin diffusing out from the MN into the skin, (d) Complete insulin is transported from MN. The streamlined plot shows the flux profile of insulin inside MN and skin. 175

Figure 7.7 Plot comparing simulation results with experimental data obtained from Liu et al. (2012), for three different amount of insulin loading (0.44, 0.25, and 0.13 IU) in MN. 176

Figure 7.8 Effect of MN properties on the time evolution of insulin plasma concentration. (a) Insulin solubilisation rate (k_{MN}) at fixed diffusion coefficient inside MN ($D_{w,MN} = 5 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$) and (b) Insulin effective diffusion coefficient inside MN at fixed insulin solubilisation rate ($k_{MN} = 1 \times 10^{-6} \text{ m}^3 \text{ mol}^{-1} \text{ s}$).
..... 178

Figure 8.1 Plot comparing the rate of drug transport from different types of polymeric MNs. The geometric and design parameters of MN and skin properties are kept constant for all three types of MN. Drug binding/retention in different domains is ignored, and drug amount is kept the same in all MNs.
..... 185

List of Tables

Table 2.1 General properties of typical polymers used in the preparation of MNs.	18
Table 2.2 Polymeric MNs used in transdermal insulin delivery.	21
Table 2.3 Examples of polymeric MNs used in TDD.	24
Table 4.1 Value of parameters used in the simulations.	69
Table 4.2 Geometry and composition parameters of MN used in the simulations.	71
Table 4.3 SMN network parameters at different hygroscopic coefficient values.	85
Table 5.1 Value of various parameters used in simulations and their source.	107
Table 8.1 Various MN and skin used in experimental and modelling approaches.	182

List of Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
DMN	Dissolving microneedle
GMRES	Generalised minimal residual method
HA	Hyaluronic acid
HFMN	Hydrogel-forming microneedle
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
IBU	Ibuprofen sodium
IU	Insulin unit
MN	Microneedle
MUMPS	Multifrontal Massively Parallel Sparse Direct Solver
OCT	Optical coherence tomography
PBS	Phosphate buffer solution
PHEMA	Poly(2-hydroxyethyl methacrylate)
PMVE/MA	Poly(methyl vinyl ether-co-maleic acid)
PTMN	Swellable microneedle
PTMN	Phase-transition microneedle
PVA	Polyvinyl alcohol
PVP	Poly(vinylpyrrolidone)

SC	<i>Stratum corneum</i>
SEM	Scanning Electron Microscopy
SRB	Sulforhodamine
TDD	Transdermal drug delivery
TEWL	Transepidermal water loss
VE	Viable epidermis
VS	Viable skin

List of Variables

\bar{M}_c	Number average molecular weight between crosslinks
C_{BD}	Concentration of bounded drug
C_D	Drug concentration
C_{FD}	Concentration of free drug
C_n	Polymer-specific characteristic ratio
C_w	Water concentration
d_p	Initial polymer density
d_w	Density of water
E_0	Elastic modulus of the MN polymer in the dry state
k_R	Drug solubilisation rate constant inside reservoir
M_∞	Mass at equilibrium time
M_t	Mass at any time t
r_H	Hydrodynamic radius
V_d	Volume of distribution
V_s	Molar volume of solvent
β_d	Material constant for drug derived from free volume theory
β_w	Material constant for water derived from free volume theory

ε_h	Hygroscopic stain
ε_σ	Strain induced due to skin mechanical properties
\bar{r}	Average radius of the openings in between polymer chains
C_b	Drug concentration in blood at any time t
C_{sat}	Concentration of water at saturation inside microneedle
D	Diffusion coefficient
E	Young's modulus
h	Height of microneedle
K_e	Elimination rate constant
k_{MN}	Drug binding rate constants in MN
K_n	Normal contact stiffness
k_{skin}	Drug binding rate constants in skin
l	Carbon-carbon bond length
M_r	Molecular weight of the polymer repeating unit
N	Number of microneedles in an array patch
N_A	Avogadro's number
P	Pressure
Q	Drug flux coming out of the unit cross-sectional area of the skin
r	Base radius of microneedle
S_b	Area of skin-blood interface

Υ	Scale factor
β	Mass fraction of drug in the MNs
β_h	Coefficient of hygroscopic expansion
ε	Strain rate
μ	Coefficient of friction
ξ	Mesh size of polymer network
τ	Tangential contact pressure
ϕ	Polymer volume fraction
χ	Flory-Huggin's interaction parameter
ν	Poisson's ratio