Medikamentenverabreichung über Mikronadeln

Description

Yin, Y., Su, W., Zhang, J., Huang, W., Li, X., Ma, H., … Wang, H.. (2021). Separable Microneedle Patch to Protect and Deliver DNA Nanovaccines against COVID-19. ACS Nano

Plain numerical DOI: 10.1021/acsnano.1c03252
DOI URL
directSciHub download

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“The successful control of coronavirus disease 2019 (covid-19) pandemic is not only relying on the development of vaccines, but also depending on the storage, transportation, and administration of vaccines. ideally, nucleic acid vaccine should be directly delivered to proper immune cells or tissue (such as lymph nodes). however, current developed vaccines are normally treated through intramuscular injection, where immune cells do not normally reside. meanwhile, current nucleic acid vaccines must be stored in a frozen state that may hinder their application in developing countries. here, we report a separable microneedle (smn) patch to deliver polymer encapsulated spike (or nucleocapsid) protein encoding dna vaccines and immune adjuvant for efficient immunization. compared with intramuscular injection, smn patch can deliver nanovaccines into intradermal for inducing potent and durable adaptive immunity. ifn-?+cd4/8+ and il-2+cd4/8+ t cells or virus specific igg are significantly increased after vaccination. moreover, in vivo results show the smn patches can be stored at room temperature for at least 30 days without decreases in immune responses. these features of nanovaccines-laden smn patch are important for developing advanced covid-19 vaccines with global accessibility.”
Lee, M. S., Pan, C. X., & Nambudiri, V. E.. (2021). Transdermal approaches to vaccinations in the COVID-19 pandemic era. Therapeutic Advances in Vaccines and Immunotherapy

Plain numerical DOI: 10.1177/25151355211039073
DOI URL
directSciHub download

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“The covid-19 pandemic has necessitated rapid vaccine development for the control of the disease. most vaccinations, including those currently approved for covid-19 are administered intramuscularly and subcutaneously using hypodermic needles. however, there are several disadvantages including pain and fear of needlesticks, the need for two doses, the need for trained health care professionals for vaccine administration, and barriers to global distribution given the need for cold supply chain. recently, transdermal techniques have been under investigation for vaccines including covid-19. microneedle

array technology utilizes multiple microscopic projections from a plate which delivers a vaccine in the form of a patch placed on the skin, allowing for painless antigen delivery with improved immune response. in this review, we discuss challenges of existing vaccines and review the literature on the science behind transdermal vaccines including microneedles, current evidence of application in infectious diseases including covid-19, and considerations for implementation and global access."
Dixon, R. V., Skaria, E., Lau, W. M., Manning, P., Birch-Machin, M. A., Moghimi, S. M., & Ng, K. W.. (2021). Microneedle-based devices for point-of-care infectious disease diagnostics. Acta Pharmaceutica Sinica B

Plain numerical DOI: 10.1016/j.apsb.2021.02.010
DOI URL
directSciHub download

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"Recent infectious disease outbreaks, such as covid-19 and ebola, have highlighted the need for rapid and accurate diagnosis to initiate treatment and curb transmission. successful diagnostic strategies critically depend on the efficiency of biological sampling and timely analysis. however, current diagnostic techniques are invasive/intrusive and present a severe bottleneck by requiring specialist equipment and trained personnel. moreover, centralised test facilities are poorly accessible and the requirement to travel may increase disease transmission. self-administrable, point-of-care (poc) microneedle diagnostic devices could provide a viable solution to these problems. these miniature needle arrays can detect biomarkers in/from the skin in a minimally invasive manner to provide (near-) real-time diagnosis. few microneedle devices have been developed specifically for infectious disease diagnosis, though similar technologies are well established in other fields and generally adaptable for infectious disease diagnosis. these include microneedles for biofluid extraction, microneedle sensors and analyte-capturing microneedles, or combinations thereof. analyte sampling/detection from both blood and dermal interstitial fluid is possible. these technologies are in their early stages of development for infectious disease diagnostics, and there is a vast scope for further development. in this review, we discuss the utility and future outlook of these microneedle technologies in infectious disease diagnosis."
Kim, E., Erdos, G., Huang, S., Kenniston, T. W., Balmert, S. C., Carey, C. D., … Gambotto, A.. (2020). Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine

Plain numerical DOI: 10.1016/j.ebiom.2020.102743
DOI URL
directSciHub download

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"Background: coronaviruses pose a serious threat to global health as evidenced by severe acute respiratory syndrome (sars), middle east respiratory syndrome (mers), and covid-19. sars coronavirus (sars-cov), mers coronavirus (mers-cov), and the novel coronavirus, previously dubbed 2019-ncov, and now officially named sars-cov-2, are the causative agents of the sars, mers, and covid-19 disease outbreaks, respectively. safe vaccines that rapidly induce potent and long-lasting virus-specific immune responses against these infectious agents are urgently needed. the coronavirus spike (s) protein, a

characteristic structural component of the viral envelope, is considered a key target for vaccines for the prevention of coronavirus infection. methods: we first generated codon optimized mers-s1 subunit vaccines fused with a foldon trimerization domain to mimic the native viral structure. in variant constructs, we engineered immune stimulants (rs09 or flagellin, as tlr4 or tlr5 agonists, respectively) into this trimeric design. we comprehensively tested the pre-clinical immunogenicity of mers-cov vaccines in mice when delivered subcutaneously by traditional needle injection, or intracutaneously by dissolving microneedle arrays (mnas) by evaluating virus specific igg antibodies in the serum of vaccinated mice by elisa and using virus neutralization assays. driven by the urgent need for covid-19 vaccines, we utilized this strategy to rapidly develop mna sars-cov-2 subunit vaccines and tested their pre-clinical immunogenicity in vivo by exploiting our substantial experience with mna mers-cov vaccines. findings: here we describe the development of mna delivered mers-cov vaccines and their pre-clinical immunogenicity. specifically, mna delivered mers-s1 subunit vaccines elicited strong and long-lasting antigen-specific antibody responses. building on our ongoing efforts to develop mers-cov vaccines, promising immunogenicity of mna-delivered mers-cov vaccines, and our experience with mna fabrication and delivery, including clinical trials, we rapidly designed and produced clinically-translatable mna sars-cov-2 subunit vaccines within 4 weeks of the identification of the sars-cov-2 s1 sequence. most importantly, these mna delivered sars-cov-2 s1 subunit vaccines elicited potent antigen-specific antibody responses that were evident beginning 2 weeks after immunization. interpretation: mna delivery of coronaviruses-s1 subunit vaccines is a promising immunization strategy ag…”
Dixon, R. V., Lau, W. M., Moghimi, S. M., & Ng, K. W.. (2020). The diagnostic potential of microneedles in infectious diseases. Precision Nanomedicine

Plain numerical DOI: 10.33218/001c.13658
DOI URL
directSciHub download

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“Graphical abstract point-of-care microneedle diagnostics abstract the coronavirus disease 2019 (covid-19) pandemic has taught us much about our weaknesses in the management of infectious disease outbreaks. a key lesson has been the need for more effective point-of-care diagnostic tools that produce not only rapid and reliable results but also facilitate decentralised testing to avoid overwhelming central test facilities when demand peaks in an outbreak. microneedle devices can be inserted painlessly into the skin to detect biomolecules in the epidermal and dermal layers. they have been used to identify biomarkers in both the interstitial fluid and capillary blood. importantly, they are amenable to self-administration. in this article, we provide an overview of existing microneedle-based diagnostic technologies and discuss how they may be built upon to provide effective diagnostic tools for infectious diseases.”
O’Shea, J., Prausnitz, M. R., & Rouphael, N.. (2021). Dissolvable microneedle patches to enable increased access to vaccines against SARS-CoV-2 and future pandemic outbreaks. Vaccines

Plain numerical DOI: 10.3390/vaccines9040320
DOI URL
directSciHub download

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“Vaccines are an essential component of pandemic preparedness but can be limited due to challenges in production and logistical implementation. while vaccine candidates were rapidly developed against severe acute respiratory syndrome coronavirus 2 (sars-cov-2), immunization campaigns remain an obstacle to achieving herd immunity. dissolvable microneedle patches are advantageous for many possible reasons: improved immunogenicity; dose-sparing effects; expected low manufacturing cost; elimination of sharps; reduction of vaccine wastage; no need for reconstitution; simplified supply chain, with reduction of cold chain supply through increased thermostability; ease of use, reducing the need for healthcare providers; and greater acceptability compared to traditional hypodermic injections. when applied to coronavirus disease 2019 (covid-19) and future pandemic outbreaks, microneedle patches have great potential to improve vaccination globally and save many lives.”
Xia, D., Jin, R., Byagathvalli, G., Yu, H., Ye, L., Lu, C. Y., … Prausnitz, M. R.. (2021). An ultra-low-cost electroporator with microneedle electrodes (ePatch) for SARS-CoV-2 vaccination. Proceedings of the National Academy of Sciences of the United States of America

Plain numerical DOI: 10.1073/pnas.2110817118
DOI URL
directSciHub download

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“Vaccination against severe acute respiratory syndrome coronavirus 2 (sars-cov-2) and other pathogens with pandemic potential requires safe, protective, inexpensive, and easily accessible vaccines that can be developed and manufactured rapidly at a large scale. dna vaccines can achieve these criteria, but induction of strong immune responses has often required bulky, expensive electroporation devices. here, we report an ultra-low-cost (<1 usd), handheld (<50 g) electroporation system utilizing a microneedle electrode array (‘epatch’) for dna vaccination against sars-cov-2. the low cost and small size are achieved by combining a thumb-operated piezoelectric pulser derived from a common household stove lighter that emits microsecond, bipolar, oscillatory electric pulses and a microneedle electrode array that targets delivery of high electric field strength pulses to the skin’s epidermis. antibody responses against sars-cov-2 induced by this electroporation system in mice were strong and enabled at least 10-fold dose sparing compared to conventional intramuscular or intradermal injection of the dna vaccine. vaccination was well tolerated with mild, transient effects on the skin. this epatch system is easily portable, without any battery or other power source supply, offering an attractive, inexpensive approach for rapid and accessible dna vaccination to combat covid-19, as well as other epidemics.”
MA, A.. (2020). Evaluation of Microneedle Drug Delivery System and Nanoparticles Use in COVID-19 Patients. International Journal of Clinical Studies and Medical Case Reports

Plain numerical DOI: 10.46998/ijcmcr.2020.02.000037
DOI URL
directSciHub download

Flynn, O., Dillane, K., Lanza, J. S., Marshall, J. M., Jin, J., Silk, S. E., … Moore, A. C.. (2021). Low adenovirus vaccine doses administered to skin using microneedle patches induce better functional antibody immunogenicity as compared to systemic injection

. Vaccines

Plain numerical DOI: 10.3390/vaccines9030299
DOI URL
directSciHub download

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“Adenovirus-based vaccines are demonstrating promising clinical potential for multiple infectious diseases, including covid-19. however, the immunogenicity of the vector itself decreases its effectiveness as a boosting vaccine due to the induction of strong anti-vector neutralizing im-munity. here we determined how dissolvable microneedle patches (dmn) for skin immunization can overcome this issue, using a clinically-relevant adenovirus-based plasmodium falciparum malaria vaccine, adhu5–pfrh5, in mice. incorporation of vaccine into patches significantly enhanced its thermostability compared to the liquid form. conventional high dose repeated immunization by the intramuscular (im) route induced low antigen-specific igg titres and high anti-vector immunity. a low priming dose of vaccine, by the im route, but more so using dmn patches, induced the most efficacious immune responses, assessed by parasite growth inhibitory activity (gia) assays. administration of low dose adhu5–pfrh5 using patches to the skin, boosted by high dose im, induced the highest antigen-specific serum igg response after boosting, the greatest skewing of the antibody response towards the antigen and away from the vector, and the highest efficacy. this study therefore demonstrates that repeated use of the same adenovirus vaccine can be highly immunogenic towards the transgene if a low dose is used to prime the response. it also provides a method of stabilizing adenovirus vaccine, in easy-to-administer dissolvable microneedle patches, permitting storage and distribution out of cold chain.”
Wang, F. Y., Chen, Y., Huang, Y. Y., & Cheng, C. M.. (2021). Transdermal drug delivery systems for fighting common viral infectious diseases. Drug Delivery and Translational Research

Plain numerical DOI: 10.1007/s13346-021-01004-6
DOI URL
directSciHub download

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“Transdermal drug delivery systems (tdds) have many advantages and represent an excellent alternative to oral delivery and hypodermic injections. tdds are more convenient and less invasive tools for disease and viral infection treatment, prevention, detection, and surveillance. the emerging development of microneedles for tdds has facilitated improved skin barrier penetration for the delivery of macromolecules or hydrophilic drugs. microneedle tdds patches can be fabricated to deliver virus vaccines and potentially provide a viable alternative vaccine modality that offers improved immunogenicity, thermostability, simplicity, safety, and compliance as well as sharp-waste reduction, increased cost-effectiveness, and the capacity for self-administration, which could improve vaccine distribution. these advantages make tdds-based vaccine delivery an especially well-suited option for treatment of widespread viral infectious diseases including pandemics. because microneedle-based bioassays employ transdermal extraction of interstitial fluid or blood, they can be used as a minimally invasive approach for surveying disease markers and providing point-of-care (poc) diagnostics. for cutaneous viral infections, tdds can provide localized treatment with high specificity and less systemic toxicity. in summary, tdds, especially those that employ microneedles, possess special attributes that

can be leveraged to reduce morbidity and mortality from viral infectious diseases. in this regard, they may have considerable positive impact as a modality for improving global health. in this article, we introduce the possible role and summarize the current literature regarding tdds applications for fighting common cutaneous or systemic viral infectious diseases, including herpes simplex, varicella or herpes zoster, warts, influenza, measles, and covid-19. graphical abstract: [figure not available: see fulltext.]." Kuwentrai, C., Yu, J., Rong, L., Zhang, B. Z., Hu, Y. F., Gong, H. R., … Xu, C.. (2021). Intradermal delivery of receptor-binding domain of SARS-CoV-2 spike protein with dissolvable microneedles to induce humoral and cellular responses in mice. Bioengineering and Translational Medicine

Plain numerical DOI: 10.1002/btm2.10202
DOI URL
directSciHub download

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"The s1 subunit of severe acute respiratory syndrome coronavirus 2 (sars-cov-2) spike protein contains an immunogenic receptor-binding domain (rbd), which is a promising candidate for the development of a potential vaccine. this study demonstrated that intradermal delivery of an s-rbd vaccine using a dissolvable microneedle skin patch can induce both significant b-cell and significant t-cell responses against s-rbd. importantly, the outcomes were comparable to that of conventional bolus injection." Ortega-Rivera, O. A., Shin, M. D., Chen, A., Beiss, V., Moreno-Gonzalez, M. A., Lopez-Ramirez, M. A., … Steinmetz, N. F.. (2021). Trivalent Subunit Vaccine Candidates for COVID-19 and Their Delivery Devices. Journal of the American Chemical Society

Plain numerical DOI: 10.1021/jacs.1c06600
DOI URL
directSciHub download

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"The covid-19 pandemic highlights the need for platform technologies enabling rapid development of vaccines for emerging viral diseases. the current vaccines target the sars-cov-2 spike (s) protein and thus far have shown tremendous efficacy. however, the need for cold-chain distribution, a prime-boost administration schedule, and the emergence of variants of concern (vocs) call for diligence in novel sars-cov-2 vaccine approaches. we studied 13 peptide epitopes from sars-cov-2 and identified three neutralizing epitopes that are highly conserved among the vocs. monovalent and trivalent covid-19 vaccine candidates were formulated by chemical conjugation of the peptide epitopes to cowpea mosaic virus (cpmv) nanoparticles and virus-like particles (vlps) derived from bacteriophage q?. efficacy of this approach was validated first using soluble vaccine candidates as solo or trivalent mixtures and subcutaneous prime-boost injection. the high thermal stability of our vaccine candidates allowed for formulation into single-dose injectable slow-release polymer implants, manufactured by melt extrusion, as well as microneedle (mn) patches, obtained through casting into micromolds, for prime-boost self-administration. immunization of mice yielded high titers of antibodies against the target epitope and s protein, and data confirms that antibodies block receptor binding and neutralize sars-cov and sars-cov-2 against infection of human cells. we present a nanotechnology vaccine platform that is stable outside the cold-chain and can be formulated into delivery devices enabling single administration or self-administration. cpmv or q? vlps could be stockpiled, and epitopes exchanged to target new mutants or

emergent diseases as the need arises."
Zhang, T., Yang, L., Yang, X., Tan, R., Lu, H., & Shen, Y.. (2021). Millimeter?Scale Soft Continuum Robots for Large?Angle and High?Precision Manipulation by Hybrid Actuation. Advanced Intelligent Systems

Plain numerical DOI: 10.1002/aisy.202000189
DOI URL
directSciHub download

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"Developing small?scale soft continuum robots with large?angle steering capacity and high?precision manipulation offers broad opportunities in various biomedical settings. however, existing continuum robots reach the bottleneck in actuation on account of the contradiction among small size, compliance actuation, large tender range, high precision, and small dynamic error. herein, a 3d?printed millimeter?scale soft continuum robot with an ultrathin hollow skeleton wall (300 ?m) and a large inner?to?outer ratio (0.8) is reported. after coating a thin ferromagnetic elastomer layer (?100–150 ?m), the proposed soft continuum robot equipped with hybrid actuation (tendon? and magnetic?driven mode) achieves large?angle (up to 100°) steering and high?precision (low to 2 ?m for static positioning) micromanipulation simultaneously. specifically, the robot implements an ultralow dynamic tracking error of ?10 ?m, which is ?30?fold improved than the state of art. combined with a microneedle/knife or nasopharyngeal swab, the robot reveals the potential for versatile biomedical applications, such as drug injection on the target tissue, diseased tissue ablation, and covid?19 nasopharyngeal sampling. the proposed millimeter?scale soft continuum robot presents remarkable advances in large?range and high?precise actuation, which provides a new method for miniature continuum robot design and finds broad applications in biomedical engineering."
Peng, K., Vora, L. K., Tekko, I. A., Permana, A. D., Domínguez-Robles, J., Ramadon, D., … Donnelly, R. F.. (2021). Dissolving microneedle patches loaded with amphotericin B microparticles for localised and sustained intradermal delivery: Potential for enhanced treatment of cutaneous fungal infections. Journal of Controlled Release

Plain numerical DOI: 10.1016/j.jconrel.2021.10.001
DOI URL
directSciHub download

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"Fungal infections affect millions of people globally and are often unreceptive to conventional topical or oral preparations because of low drug bioavailability at the infection site, lack of sustained therapeutic effect, and the development of drug resistance. amphotericin b (amb) is one of the most potent antifungal agents. it is increasingly important since fungal co-infections associated with covid-19 are frequently reported. amb is only administered via injections (iv) and restricted to life-threatening infections due to its nephrotoxicity and administration-related side effects. in this work, we introduce, for the first time, dissolving microneedle patches (dmp) loaded with micronised particles of amb to achieve localised and long-acting intradermal delivery of amb for treatment of cutaneous fungal infections. amb was pulverised with poly (vinyl alcohol) and poly (vinyl pyrrolidone) to form micronised particles-loaded gels, which were then cast into dmp moulds to form the tips. the mean particle size of

amb in amb dmp tips after pulverisation was 1.67 ± 0.01 ?m. this is an easy way to fabricate and load microparticles into dmp, as few steps are required, and no organic solvents are needed. amb had no covalent chemical interaction with the excipients, but the crystallinity of amb was reduced in the tips. amb was completely released from the tips within 4 days in vitro. amb dmp presented inhibition of candida albicans (ca) and the killing rate of amb dmp against ca biofilm inside porcine skin reached 100% within 24 h. amb dmp were able to pierce excised neonatal porcine skin at an insertion depth of 301.34 ± 46.86 ?m. ex vivo dermatokinetic and drug deposition studies showed that amb was mainly deposited in the dermis. an in vivo dermatokinetic study revealed that the area under curve (auc0-inf) values of amb dmp and iv (fungizone® bolus injection 1 mg/kg) groups were 8823.0 d??g/g and 33.4 d??g/g, respectively (264-fold higher). amb remained at high levels (219.07 ± 102.81 ?g/g or more) in the skin until 7 days after the application of amb dmp. pharmacokinetic and biodistribution studies showed that amb concentration in plasma, kidney, liver, and spleen in the amb dmp group was significantly lower than that in the iv group. accordingly, this system addressed the systemic side effects of intravenous injection of amb and localised the drug inside the skin for a week. this work establishes a novel, easy and effective method for long-acting and localise…"
Qin, M., Du, G., & Sun, X.. (2021). Recent Advances in the Noninvasive Delivery of mRNA. Accounts of Chemical Research

Plain numerical DOI: 10.1021/acs.accounts.1c00493
DOI URL
directSciHub download

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"ConspectusOver the past two decades, research on mrna-based therapies has exploded, mainly because of the inherent advantages of mrna, including a low integration probability, transient expression, and simple and rapid in vitro transcription production approaches. in addition, thanks to improved stability and reduced immunogenicity by advanced strategies, the application of mrna has expanded from protein replacement therapy to vaccination, gene editing and other fields, showing great promise for clinical application. recently, with the successive launch of two mrna-based covid-19 vaccines, mrna technology has attracted an enormous amount of attention from scientific researchers as well as pharmaceutical companies. because of the large molecular weight, hydrophilicity, and highly negative charge densities of mrna, it is difficult to overcome the intracellular delivery barriers. therefore, various delivery vehicles have been developed to achieve more effective mrna delivery. in general, conventional mrna administration methods are based on injection strategies, including intravenous, intramuscular, intradermal, and subcutaneous injections. although these routes circumvent the absorption barriers to some extent, they bring about injection-related concerns such as safety issues, pain, low compliance, and difficulty in repeated dosing, increasing the need to explore alternative strategies for noninvasive delivery. the ideal noninvasive delivery systems are featured with easy to use, low risks of infection, and good patient compliance. at the same time, they allow patients to self-administer, reducing reliance on professional healthcare workers and interference with bodily functions and daily life. in particular, the noninvasive mucosal delivery of mrna vaccines can induce mucosal immune responses, which are important for resisting pathogens infected through mucosal routes.because of the potential clinical benefits mentioned above, we detailed the existing strategies for the noninvasive delivery of mrna in this review, including delivery via the nasal, pulmonary, vaginal, and transdermal routes. first, we discussed the unique strengths and biological hindrances of each route on the basis of physiology. next, we comprehensively summarized the research progress

reported so far and analyzed the technologies and delivery vehicles used, hoping to provide some references for further explorations. among these noninvasive routes, nasal and pulmonary delivery are the …"

Mikronadeln, Mikronadelpflaster oder Mikroarray-Pflaster sind medizinische Geräte im Mikromaßstab, die zur Verabreichung von Impfstoffen, Arzneimitteln und anderen therapeutischen Wirkstoffen verwendet werden.[2] Während Mikronadeln ursprünglich für die transdermale Verabreichung von Arzneimitteln erforscht wurden, wurde ihre Verwendung auf die intraokulare, vaginale, transunguale, kardiale, vaskuläre, gastrointestinale und intracochleäre Verabreichung von Arzneimitteln ausgeweitet. [3] [4] [5] Mikronadeln werden mit verschiedenen Methoden hergestellt, in der Regel mit photolithografischen Verfahren oder durch Mikroformen[6], bei denen mikroskopische Strukturen in Harz oder Silizium geätzt werden, um Mikronadeln zu gießen. Mikronadeln werden aus verschiedenen Materialien wie Silizium, Titan, rostfreiem Stahl und Polymeren hergestellt.[7][1] Einige Mikronadeln bestehen aus einem Medikament, das dem Körper zugeführt werden soll, sind aber so geformt, dass sie die Haut durchdringen. Die Mikronadeln unterscheiden sich in Größe, Form und Funktion, werden aber alle als Alternative zu anderen Verabreichungsmethoden wie der herkömmlichen Injektionsnadel oder anderen Injektionsgeräten verwendet.

Mikronadeln werden in der Regel durch eine einzelne Nadel oder kleine Arrays appliziert. Bei den verwendeten Arrays handelt es sich um eine Ansammlung von Mikronadeln, die von einigen wenigen bis zu mehreren Hundert reichen und an einem Applikator, manchmal einem Pflaster oder einem anderen festen Stanzgerät, befestigt sind. Die Arrays werden auf die Haut des Patienten aufgebracht und erhalten Zeit, um die wirksame Verabreichung von Medikamenten zu ermöglichen. Mikronadeln stellen für Ärzte eine einfachere Methode dar, da ihre Anwendung weniger Schulung erfordert und sie nicht so gefährlich sind wie andere Nadeln. Dadurch wird die Verabreichung von Arzneimitteln an Patienten sicherer und weniger schmerzhaft, während gleichzeitig einige der Nachteile anderer Formen der Verabreichung von Arzneimitteln vermieden werden, wie z. B. das Infektionsrisiko, die Produktion von Sondermüll oder die Kosten.
Inhalt

Hintergrund

Hauptartikel: Mikroinjektion

Mikronadeln wurden erstmals 1998 in einer Arbeit der Forschergruppe um Mark Prausnitz am Georgia Institute of Technology erwähnt, in der nachgewiesen wurde, dass Mikronadeln die oberste Schicht (Stratum corneum) der menschlichen Haut durchdringen können und daher für die transdermale Verabreichung von therapeutischen Wirkstoffen geeignet sind.[8] Spätere Forschungen zur Verabreichung von Medikamenten über Mikronadeln haben die medizinischen und kosmetischen Anwendungen dieser Technologie durch ihr Design untersucht. In dieser frühen Arbeit wurde die Möglichkeit untersucht, Mikronadeln in Zukunft für Impfungen zu verwenden. Seitdem haben Forscher die Verabreichung von Insulin, Impfstoffen, entzündungshemmenden Mitteln und anderen Arzneimitteln über Mikronadeln untersucht. In der Dermatologie werden Mikronadeln zur Behandlung von Narben mit Hautrollern eingesetzt.

Das Hauptziel eines jeden Mikronadeldesigns ist es, die äußerste Schicht der Haut, das Stratum corneum (10-15?m), zu durchdringen.[9] Die Mikronadeln sind lang genug, um das Stratum corneum zu durchdringen, aber nicht so lang, dass sie Nerven stimulieren, die sich tiefer im Gewebe befinden und daher keine oder nur geringe Schmerzen verursachen.[8]

Die Forschung hat gezeigt, dass es eine Grenze für die Art von Medikamenten gibt, die durch intakte Haut verabreicht werden können. Nur Verbindungen mit einem relativ geringen Molekulargewicht, wie das häufige Allergen Nickel (130 Da),[10] können die Haut durchdringen. Verbindungen mit einem Gewicht von mehr als 500 Da können die Haut nicht durchdringen.[9]

Arten von Mikronadeln

Seit ihrer Entwicklung im Jahr 1998 wurden mehrere Fortschritte in Bezug auf die verschiedenen Arten von Mikronadeln gemacht, die hergestellt werden können. Die 4 Haupttypen von Mikronadeln sind fest, hohl, beschichtet und auflösbar/auflösend[2].
Festkörper

Diese Art von Array ist als zweiteiliges System konzipiert; das Mikronadel-Array wird zunächst auf die Haut aufgebracht, um mikroskopisch kleine Vertiefungen zu erzeugen, die gerade tief genug sind, um die äußerste Hautschicht zu durchdringen, und dann wird das Arzneimittel über ein transdermales Pflaster appliziert. Feste Mikronadeln werden von Dermatologen bereits in der Kollageninduktionstherapie eingesetzt, einer Methode, bei der durch wiederholtes Einstechen von Mikronadeln in die Haut die Expression und Ablagerung der Proteine Kollagen und Elastin in der Haut angeregt wird.[11]

Bei einer neueren Anpassung des Mikronadeldesigns kapseln auflösbare Mikronadeln das Arzneimittel in ein ungiftiges Polymer ein, das sich auflöst, sobald es sich in der Haut befindet.[1] Dieses Polymer würde es ermöglichen, das Arzneimittel in die Haut einzubringen, und könnte im Körper abgebaut werden. Pharmaunternehmen und Forscher haben begonnen, Polymere wie Fibroin zu untersuchen und einzusetzen, ein Protein auf Seidenbasis, das zu Strukturen wie Mikronadeln geformt und im Körper aufgelöst werden kann[12].

Vorteile

Die Verwendung von Mikronadeln hat viele Vorteile, von denen der größte der verbesserte Komfort für die Patienten ist. Nadelphobie kann sowohl Erwachsene als auch Kinder betreffen und manchmal zu Ohnmachtsanfällen führen. Der Vorteil von Mikronadel-Arrays ist, dass sie die Angst der Patienten vor einer Injektionsnadel verringern. Neben der Verbesserung des psychologischen und emotionalen Komforts sind Mikronadeln nachweislich wesentlich weniger schmerzhaft als herkömmliche Injektionen.[9] In einigen Studien wurden die Ansichten von Kindern zur Blutentnahme mit Mikronadeln aufgezeichnet, und es wurde festgestellt, dass die Patienten bereitwilliger waren, wenn sie mit einem weniger schmerzhaften Verfahren konfrontiert wurden als mit der herkömmlichen Blutentnahme mit Nadeln. Mikronadeln sind auch für Ärzte von Vorteil, da sie weniger gefährlichen Abfall produzieren als Nadeln und im Allgemeinen einfacher zu handhaben sind. Mikronadeln sind auch kostengünstiger als Nadeln, da sie weniger Material benötigen und das verwendete Material billiger ist als das Material von Injektionsnadeln.

Mikronadeln bieten eine neue Chance für die Gesundheitsversorgung zu Hause und in der Gemeinde. Einer der größten Nachteile herkömmlicher Nadeln ist der gefährliche Abfall, den sie produzieren, was die Entsorgung zu einem ernsten Problem für Ärzte und Krankenhäuser macht. Für Patienten, die sich regelmäßig Medikamente zu Hause verabreichen müssen, kann die Entsorgung zu einem Umweltproblem werden, wenn die Nadeln im Müll landen. Auflösbare oder schwellbare Mikronadeln würden denjenigen, die nur begrenzt in der Lage sind, ein Krankenhaus aufzusuchen, die Möglichkeit geben, sich bequem zu Hause Medikamente zu verabreichen, obwohl die Entsorgung von festen oder hohlen Mikronadeln immer noch ein Risiko für Nadelstichverletzungen oder durch Blut übertragbare Krankheitserreger darstellen könnte[1].

Ein weiterer Vorteil von Mikronadeln ist die geringere Invasion von Mikroorganismen in die Einstichstellen.[1][9] Bei herkömmlichen Injektionsmethoden können Einstichwunden bis zu 48 Stunden nach der Behandlung zurückbleiben. Damit bleibt ein großes Zeitfenster für das Eindringen schädlicher Bakterien in die Haut. Mikronadeln verletzen die Haut nur bis zu einer Tiefe von 10-15 ?m, was es den Bakterien erschwert, in den Blutkreislauf einzudringen, und dem Körper eine kleinere Wunde zum Reparieren gibt.[6] Weitere Forschung ist erforderlich, um die Arten von Bakterien zu bestimmen, die in der Lage sind, die flache Einstichstelle von Mikronadeln zu überwinden.

Nachteile

Es gibt einige Bedenken darüber, wie Ärzte sicher sein können, dass das gesamte Medikament oder der Impfstoff in die Haut gelangt ist, wenn Mikronadeln eingesetzt

werden. Sowohl bei hohlen als auch bei beschichteten Mikronadeln besteht das Risiko, dass das Medikament nicht richtig in die Haut eindringt und nicht wirksam ist. Beide Arten von Mikronadeln können entweder durch eine Beschädigung der Mikronadel oder durch eine unsachgemäße Anwendung durch den Arzt in die Haut einer Person eindringen[13][9]. Deshalb ist es wichtig, dass die Ärzte in der korrekten Anwendung der Arrays geschult werden.

Ein weiteres Problem besteht darin, dass bei unsachgemäßer Anwendung der Arrays Fremdmaterial im Körper zurückbleiben könnte. Obwohl bei Mikronadeln ein geringeres Infektionsrisiko besteht, sind die Arrays aufgrund ihrer geringen Größe zerbrechlicher als eine typische Injektionsnadel, so dass die Gefahr besteht, dass sie abbrechen und in der Haut verbleiben. Einige der für die Konstruktion der Mikronadeln verwendeten Materialien, wie z. B. Titan, können vom Körper nicht absorbiert werden, und Bruchstücke der Nadeln würden Reizungen verursachen.

Es gibt nur eine begrenzte Menge an Literatur zum Thema Medikamentenabgabe über Mikronadeln, da die aktuelle Forschung noch erforscht, wie man wirksame Nadeln herstellen kann.
Forschung und Anwendungen

Forscher am MIT unter der Leitung von Ana Jaklenec entwickeln eine Technologie zur Verabreichung von Impfstoffen und zur Hinterlassung eines unsichtbaren Impfpasses beim Patienten. Diese Forschungsarbeiten werden von zahlreichen Einrichtungen finanziert, darunter die Bill & Melinda Gates Foundation und das Koch-Institut[14].

Es wird sogar erwogen, die neue Technologie zur Überwachung der Impfungen von Reisenden einzusetzen, um die Ausbreitung von Infektionskrankheiten zu verhindern. Die unsichtbare Markierung würde an den Einreisehäfen gescannt werden, um den Personenverkehr zu ermöglichen und gleichzeitig die Verbreitung von Viren zu kontrollieren[15].

Einsatz bei der COVID-19-Pandemie

Mikronadeln bieten ein bequemes System zur Verabreichung von Impfstoffen an eine große Bevölkerungsgruppe, ohne dass eine ausgeklügelte Forschungsinfrastruktur erforderlich ist, und die Möglichkeit der Selbstverabreichung. Darüber hinaus sind auflösbare Mikronadelpflaster ein äußerst praktisches System für die Verabreichung von Impfstoffen, da sich die Nadeln in der Haut auflösen und keine scharfen biomedizinischen Abfälle hinterlassen (im Gegensatz zu herkömmlichen subkutanen/intramuskulären Impfsystemen), was die Entsorgung erleichtert.[16][17]

Mehrere Forschungsteams haben Mikronadeln für die Verabreichung verschiedener Arten von Impfstoffen gegen das SARS-CoV-2-Virus entwickelt oder sind dabei, diese zu entwickeln, um die COVID-19-Pandemie zu beenden[18].

en.wikipedia.org/wiki/Microneedle_drug_delivery
Übersetzt mit www.DeepL.com/Translator (kostenlose Version)

Dathathri, E., Lal, S., Mittal, M., Thakur, G., & De, S.. (2020). Fabrication of low-cost composite polymer-based micro needle patch for transdermal drug delivery

. Applied Nanoscience (Switzerland)

Plain numerical DOI: 10.1007/s13204-019-01190-3
DOI URL
directSciHub download

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“Microneedle delivery patches are an emerging technology to attain painless and sustained delivery through the epidermis of the skin. this study is unique in its attempt to develop polymeric microneedles embedded with drug. special polymer chitosan with hydrogel forming capability is cross-linked with pva, a water-soluble polymer with excellent film strengthening ability and loaded with model drug diclofenac sodium. the microneedle patch was fabricated by pouring the chitosan-pva solution (ratio 1:6) on negative replica of master mold, which upon drying was peeled off to result in the composite film. the film of chitosan-pva in the ratio 1:6 when tested for mechanical behavior exhibited improved mechanical strength owing to use of pva, the presence of effective cross-linking of pva with chitosan was further verified with ftir. the release from drug-loaded needles was promising, as cross-linking with pva enabled a sustained drug release of 20.17% at the end of 30 h. the release followed the higuchi model with fickian diffusion, indicating a swelling-dependent release. the microneedle prepared using a composite of chitosan-pva showed promising results indicating its potential to be used as a drug eluting transdermal patch.”
Yoon, H. S., Lee, S. J., Park, J. Y., Paik, S. J., & Allen, M. G.. (2014). A non-enzymatic micro-needle patch sensor for free-cholesterol continuous monitoring. In Proceedings of IEEE Sensors

Plain numerical DOI: 10.1109/ICSENS.2014.6985005
DOI URL
directSciHub download

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“A patch type non-enzymatic free-cholesterol sensor was newly developed for continuous monitoring by using stainless steel based micro-needle patch and nanoporous platinum (npt) sensing electrodes. the formed micro-needle patch was coated with parylene/gold/parylene film and selectively dry-etched to form the gold electrodes at the tips of micro-needles. the bare gold tips were finally electroplated with nanoporous platinum. the sensor was then characterized and analyzed by using cyclic voltammetry and chronoamperometry measurement techniques. the fabricated sensor exhibited high sensitivity of 305na/mm•cm2 and correlation coefficient of 0.964 in 0.1m pbs (ph 7.4). in the recovery test, recovery rate was more than 89%.”
Srinivas, P., Shanthi, C. L., & Sadanandam, M.. (2010). Micro Needle Patches in Drug Delivery – A Review. International Journal of Pharmacy & Technology

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“Drugs are administered by using different drug delivery systems. a number of drug delivery systems have evolved over the years. in the last 20 years tdds (transdermal drug delivery system) has been growing at a rapid pace. now the micro needles are being developed as a novel drug delivery system. the micro needle skin patch system is also a drug delivery system, which will be used transdermally.

the success of tdd has severely limited by the inability of most drugs to enter the skin at therapeutical useful rates. thus, the use of micro-needle patches in increasing skin permeability has been proposed and shown to dramatically increase in transdermal delivery, especially for macromolecules. using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. most drug delivery studies have emphasized microneedles, which have been shown to increase the skin permeability to a broad range of molecules and nanoparticles invitro. this review briefly deals with types, mode of drug delivery, coating and applications of microneedle patches. overall the microneedle skin patches are prone to be a very versatile drug delivery technology, allowing easy and reproducible delivery to skin."
Mogusala, N. R., Devadasu, V. R., & Venisetty, R. K.. (2015). Fabrication of Microneedle Molds and Polymer Based Biodegradable Microneedle Patches: A Novel Method. American Journal of Drug Delivery and Therapeutics

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"Objective: microneedleis a micro sized needle-like structure which has the ability to pierce the skin in a non-invasive and painless way. the present research work aims to design microneedle molds in a novel way and fabricate and characterize biodegradable polymer based micro-needle patch utilizing polymer casting. methods: fabrication of polymer patch involved two steps, one is to fabricate microneedle array mold and the other is to prepare biodegradable polymeric microneedle patch using the molds. molds are prepared by manually piercing the mixture of resin and hydrate (emseal) using needles having micro tips and patches are prepared using polymer solution. characterization of microneedle patch was done using scanning electron microscope and skin piercing ability was understood from histological studies of the rat skin. results: the micro-needles on the patch were found to be uniform in size and shape, with concentric circular features, the size of the microneedle tip was found to be between 20-50 µm and base around 200 µm and the shape was found to be conical with sharp tip. the micro-needles showed good penetration in to the skin which was observed by the histological studies performed using rat skin. conclusion: the present study demonstrates that the microneedle molds can be prepared using resins and microneedles can be developed using polymer casting method. the developed microneedles showed comparable structural features with those reported in the literature. these microneedles possessed good mechanical strength and can pierce the rat skin."
Wang, J., & Pickwell-Macpherson, E.. (2020). Terahertz Imaging for Topical and Micro/Nano Needle Patch Drug Delivery. In International Conference on Infrared, Millimeter, and Terahertz Waves, IRMMW-THz

Plain numerical DOI: 10.1109/IRMMW-THz46771.2020.9370912
DOI URL
directSciHub download

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"We demonstrate the ability of thz imaging to evaluate the efficacy of transdermal drug delivery. effects of transdermal drug delivery by topical and micro/nano-needle patch methods are measured. our results prove that thz imaging is able to monitor the improved drug delivery efficacy given by a nanoneedle patch."

Rapoport, A. M., & McAllister, P.. (2020). The Headache Pipeline: Excitement and Uncertainty. Headache

Plain numerical DOI: 10.1111/head.13728
DOI URL
directSciHub download

Show/hide publication abstract

“There are many new treatment options available for migraine and more are coming. three calcitonin gene-related peptide (cgrp) antagonist monoclonal antibodies have been approved and a 4th is due in early 2020. small molecule cgrp receptor-blocking oral compounds, both for acute care and prevention, are also coming. four neurostimulators are available, with others on the way. new acute treatments coming soon include the 5ht1f agonist lasmiditan, a zolmitriptan intradermal micro-needle patch, and a nasal mist sumatriptan with a permeability enhancer. farther out, three novel dihydroergotamine delivery systems, and a liquid-filled capsule of celecoxib show early promise. a new, safer form of methysergide is in the works, as is a longer-duration onabotulinumtoxina. as always with new products, questions regarding safety, tolerability, cost, and insurance coverage will need to be addressed. despite these concerns and uncertainties, a robust headache treatment pipeline is good for patients who are not satisfied with the results of their treatment and/or cannot tolerate existing treatments.”
Kwon, S. Y.. (2004). In vitro evaluation of transdermal drug delivery by a micro-needle patch. Controlled Release Society 31st Annual Meeting …

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“INTRODUCTION: there has been rapid progress in molecular biology, to identify and prepare specific peptide, protein and oligonucleotide drugs and vaccines to treat or prevent disease with minimal side effects. however, concomitant progress in delivery systems for these drugs …”
Ha, J. M., Lim, C. A., Han, K., Ha, J. C., Lee, H. E., Lee, Y., … Im, M.. (2017). The effect of micro-spicule containing epidermal growth factor on periocular wrinkles. Annals of Dermatology

Plain numerical DOI: 10.5021/ad.2017.29.2.187
DOI URL
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“Background: micro-needle patches have been recently used to increase skin permeability, which improves drug delivery, and for cosmetic purposes. however, these patches may often have limited efficacy due to insufficient skin penetration and reduced compliance caused by discomfort. objective: we evaluated the efficacy and the safety of soluble micro-spicule containing epidermal growth factor (ms-egf) for the treatment of periocular wrinkles. methods: twenty healthy volunteers aged 33 to 54 years were enrolled in a randomized, controlled, split-face study. for 4 weeks, a periocular wrinkle was treated daily with either a soluble ms-egf cream or a cream containing egf alone. all subjects underwent 8 weeks of follow-up. efficacy was assessed using an ultrasonic measurement of dermal depth and density, digital skin image analysis, 5-point photonumeric scale for periocular wrinkles and subjective satisfaction. results: ms-egf group showed statistically significant increase of dermal depth

and density compared to egf alone group after 4 and 8 weeks. in addition, there was a marked improvement shown in clinical and 3-dimensional skin image in ms-egf group. the treatments were well-tolerated; no significant side-effect was noted. conclusion: the ms-egf formulation may represent an effective and biocompatible advance in the treatment of periocular wrinkles."
Kwon, S. Y., & Oh, S.. (2005). Rapid Intradermal Drug Delivery by a Dissolvable Micro-Needle Patch. … Release Society 32 Nd Annual Meeting

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"It is generally recognized that skin immunization is more effective and more efficient for vaccination 1-2 than standard intramuscular or subcutaneous syringe injection. it is the langerhans cells in the skin that initiate the immune response. the dissolvable transdermal micro – needle …"
Jamaledin, R., Di Natale, C., Onesto, V., Taraghdari, Z. B., Zare, E. N., Makvandi, P., … Netti, P. A.. (2020). Progress in microneedle-mediated protein delivery. Journal of Clinical Medicine

Plain numerical DOI: 10.3390/jcm9020542
DOI URL
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"The growing demand for patient-compliance therapies in recent years has led to the development of transdermal drug delivery, which possesses several advantages compared with conventional methods. delivering protein through the skin by transdermal patches is extremely difficult due to the presence of the stratum corneum which restricts the application to lipophilic drugs with relatively low molecular weight. to overcome these limitations, microneedle (mn) patches, consisting of micro/miniature-sized needles, are a promising tool to perforate the stratum corneum and to release drugs and proteins into the dermis following a non-invasive route. this review investigates the fabrication methods, protein delivery, and translational considerations for the industrial scaling-up of polymeric mns for dermal protein delivery."
Reddy Mogusala, N., Ratnam Devadasu, V., & Kumar Venisetty, R.. (2015). American Journal of Drug Delivery and Therapeutics Fabrication of Microneedle Molds and Polymer Based Biodegradable Microneedle Patches: A Novel Method. American Journal of Drug Delivery and Therapeutics

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"Objective: microneedleis a micro sized needle-like structure which has the ability to pierce the skin in a non-invasive and painless way. the present research work aims to design microneedle molds in a novel way and fabricate and characterize biodegradable polymer based micro-needle patch utilizing polymer casting. methods: fabrication of polymer patch involved two steps, one is to fabricate microneedle array mold and the other is to prepare biodegradable polymeric microneedle patch using the molds. molds are prepared by manually piercing the mixture of resin and hydrate (emseal) using needles having micro tips and patches are prepared using polymer solution. characterization of microneedle patch was done using scanning electron microscope and skin piercing ability was understood from histological studies of the rat skin. results: the micro-needles on the patch were found to be uniform in size and shape, with concentric circular features, the size of the microneedle tip was found to be between 20-50 µm and base around 200 µm and the shape was found to be conical with

sharp tip. the micro-needles showed good penetration in to the skin which was observed by the histological studies performed using rat skin. conclusion: the present study demonstrates that the microneedle molds can be prepared using resins and microneedles can be developed using polymer casting method. the developed microneedles showed comparable structural features with those reported in the literature. these microneedles possessed good mechanical strength and can pierce the rat skin."
Kwon, S. Y.. (2006). Acne Treatment by a Dissolvable Microneedle Patch. Controlled Release Society 33 St Annual Meeting

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… "… Release liner acne treatment by a dissolvable micro – needle patch sung-yun kwon theraject inc., 39270 paseo padre #112, fremont, ca 94538, usa abstract: the versatile therajectmattm, dissolvable micro – needle patch , contains api in an inert gras matrix. …"
Song, J. E., Jun, S. H., Park, S. G., & Kang, N. G.. (2020). A semi-dissolving microneedle patch incorporating TEMPO-oxidized bacterial cellulose nanofibers for enhanced transdermal delivery. Polymers

Plain numerical DOI: 10.3390/POLYM12091873
DOI URL
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"Although dissolving microneedles have garnered considerable attention as transdermal delivery tools, insufficient drug loading remains a challenge owing to their small dimension. herein, we report a one-step process of synthesizing semi-dissolving microneedle (sdmn) patches that enable effective transdermal drug delivery without loading drugs themselves by introducing tempo-oxidized bacterial cellulose nanofibers (tobcns), which are well dispersed, while retaining their unique properties in the aqueous phase. the sdmn patch fabricated by the micro-molding of a tobcn/hydrophilic biopolymer mixture had a two-layer structure comprising a water-soluble needle layer and a tobcn-containing insoluble backing layer. moreover, the sdmn patch, which had a hole in the backing layer where tobcns are distributed uniformly, could offer novel advantages for the delivery of large quantities of active ingredients. in vitro permeation analysis confirmed that tobcns with high water absorption capacity could serve as drug reservoirs. upon sdmn insertion and the application of drug aqueous solution through the drug inlet hole, the tobcns rapidly absorbed the solution and supplied it to the needle layer. simultaneously, the needle layer dissolved in body fluids and the drug solution to form micro-channels, which enabled the delivery of larger quantities of drugs to the skin compared to that enabled by solution application alone."
Lee, S. J., Yoon, H. S., Xuan, X., Park, J. Y., Paik, S. J., & Allen, M. G.. (2016). A patch type non-enzymatic biosensor based on 3D SUS micro-needle electrode array for minimally invasive continuous glucose monitoring. Sensors and Actuators, B: Chemical

Plain numerical DOI: 10.1016/j.snb.2015.08.013
DOI URL
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“We developed a new patch-shaped enzyme free biosensor using a micro-needle array with pt black sensing electrode layer for painless continuous glucose monitoring applications. we fabricated the micro-needle array using a bulk micromachining technique and commercial stainless steel 316l grade substrate. pt black and ag/agcl were then electroplated on the tip of each micro-needle as working and counter/reference electrodes of the sensor, respectively. the fabricated micro-needle was 650 ?m high and 150 ?m wide. we used 48 and 24 micro-needles for the working electrode and counter/reference electrode, respectively. the measured sensitivity was 1.62 ?a mm-1 with high linearity of 0.9939, and was obtained within 13 sec, in glucose concentrations ranging up to 36 mm. the biosensor also exhibited a low detection limit of 50 ?m. we tested the sensor under pbs solution over a period of 6 days. then we partially inserted the sensor into a rabbit, to monitor the interstitial glucose level. we then induced change of interstitial glucose concentration by oral glucose tolerance test. although we expected the sensor to perform for more than 6 days, it performed for just 4 days as a sensor, due to bio fouling.”
Reddy Mogusala, N., Ratnam Devadasu, V., & Kumar Venisetty, R.. (2015). Fabrication of Microneedle Molds and Polymer Based Biodegradable Microneedle Patches: A Novel Method. American Journal of Drug Delivery and Therapeutics

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“Objective: microneedleis a micro sized needle-like structure which has the ability to pierce the skin in a non-invasive and painless way. the present research work aims to design microneedle molds in a novel way and fabricate and characterize biodegradable polymer based micro-needle patch utilizing polymer casting. methods: fabrication of polymer patch involved two steps, one is to fabricate microneedle array mold and the other is to prepare biodegradable polymeric microneedle patch using the molds. molds are prepared by manually piercing the mixture of resin and hydrate (emseal) using needles having micro tips and patches are prepared using polymer solution. characterization of microneedle patch was done using scanning electron microscope and skin piercing ability was understood from histological studies of the rat skin. results: the micro-needles on the patch were found to be uniform in size and shape, with concentric circular features, the size of the microneedle tip was found to be between 20-50 µm and base around 200 µm and the shape was found to be conical with sharp tip. the micro-needles showed good penetration in to the skin which was observed by the histological studies performed using rat skin. conclusion: the present study demonstrates that the microneedle molds can be prepared using resins and microneedles can be developed using polymer casting method. the developed microneedles showed comparable structural features with those reported in the literature. these microneedles possessed good mechanical strength and can pierce the rat skin.”
Alkhiro, A. R., & Ghareeb, M. M.. (2020). Formulation and evaluation of iornoxicam as dissolving microneedle patch. Iraqi Journal of Pharmaceutical Sciences

Plain numerical DOI: 10.31351/VOL29ISS1PP184-194
DOI URL
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“The objective of the study was to develop microneedle (mn) patch, with suitable properties to ensure the delivery of a therapeutic level of lornoxicam (lxm) in a period suitable to replace parenteral administration in patients, especially those who fear needles. the used polymers were cold water-soluble polyvinyl alcohol (pva) and polyvinylpyrrolidone (pvp) of low molecular weight with peg 400 as plasticizer and tween 80 (to enhance the release) using micro molding technique. patches were studied for needle morphology, drug content, axial fracture force measurement and drug release while the optimized formulas were further subjected to ph measurement, folding endurance, ex vivo permeation study, histopathology study, stability study and compatibility study. the patch with 11:1 ratio of pva to pvp, 30% solid content, 5% peg 400 and 3% tween 80 resulted in axial needle fracture force value of (1.35 n) which is suitable for skin penetration. the release was fast with almost 100% of drug released in 60 minutes. the permeation was enhanced significantly with a steady state flux of about 3.1 times that of the solution. the lag time of mn is shorter in comparison with ordinary patch. histopathology studies demonstrated the safety of the formulation, both stability studies and compatibility studies showed the suitability of the formulation. the results indicated that lxm microneedle patch could enhance drug permeation while achieving fast and painless administration. copyrights”
Lee, S., Lahiji, S. F., Jang, J., Jang, M., & Jung, H.. (2019). Micro-pillar integrated dissolving microneedles for enhanced transdermal drug delivery. Pharmaceutics

Plain numerical DOI: 10.3390/pharmaceutics11080402
DOI URL
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“The dissolving microneedle (dmn) patch is a transdermal delivery system, containing arrays of micro-sized polymeric needles capable of encapsulating therapeutic drugs within their matrix and releasing them into the skin. however, the elastic properties of the skin prevent dmns from complete insertion and accurate delivery of encapsulated compounds into the skin. moreover, the adhesive materials used in patches may cause skin irritation, inflammation, and redness. therefore, we developed a patchless, micro-pillar integrated dmn (p-dmn) that is simple to fabricate and enhances transdermal drug delivery compared with traditional dmn patches. the micro-pillars were made of poly methyl methacrylate at a height of 300 ?m and a base diameter of 500 ?m. to fabricate p-dmns, we employed hyaluronic acid, which is a widely used derma filler and plays a role in tissue re-epithelialization. we demonstrate that utilizing p-dmns significantly improves the delivery efficiency of an encapsulated drug surrogate (91.83% ± 7.75%) compared with traditional dmns (64.86% ± 8.17%). interestingly, p-dmns remarkably increase the skin penetration accuracy rate of encapsulated drugs, up to 97.78% ± 222%, compared with 44.44% ± 7.85% in traditional dmns. our findings suggest that p-dmns could serve as a highly accurate and efficient platform for transdermal delivery of various types of micro- and macro-biomolecules.”

Mazzara, J. M., Ochyl, L. J., Hong, J. K. Y., Moon, J. J., Prausnitz, M. R., & Schwendeman, S. P.. (2019). Self-healing encapsulation and controlled release of vaccine antigens from PLGA microparticles delivered by microneedle patches. Bioengineering & Translational Medicine

Plain numerical DOI: 10.1002/btm2.10103
DOI URL
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“There is an urgent need to reduce reliance on hypodermic injections for many vaccines to increase vaccination safety and coverage. alternative approaches include controlled release formulations , which reduce dosing frequencies, and utilizing alternative delivery devices such as microneedle patches (mnps). this work explores development of controlled release microparti-cles made of poly (lactic-co-glycolic acid) (plga) that stably encapsulate various antigens though aqueous active self-healing encapsulation (ase). these microparticles are incorporated into rapid-dissolving mnps for intradermal vaccination. plga microparticles containing alhydrogel are loaded with antigens separate from micro-particle fabrication using ase. this avoids antigen expsoure to many stressors. the microparti-cles demonstrate bi-phasic release, with initial burst of soluble antigen, followed by delayed release of alhydrogel-complexed antigen over approximately 2 months in vitro. for delivery, the microparticles are incorporated into mnps designed with pedestals to extend functional micro-needle length. these microneedles readily penetrate skin and rapidly dissolve to deposit micro-particles intradermally. microparticles remain in the tissue for extended residence, with mnp-induced micropores resealing readily. in animal models, these patches generate robust immune responses that are comparable to conventional administration techniques. this lays the framework for a versatile vaccine delivery system that could be self-applied with important logistical advantages over hypodermic injections.”
Corbett, H. J., Fernando, G. J. P., Chen, X., Frazer, I. H., & Kendall, M. A. F.. (2010). Skin vaccination against cervical cancer associated human papillomavirus with a novel micro-projection array in a mouse model. PLoS ONE

Plain numerical DOI: 10.1371/journal.pone.0013460
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“Background: better delivery systems are needed for routinely used vaccines, to improve vaccine uptake. many vaccines contain alum or alum based adjuvants. here we investigate a novel dry-coated densely-packed micro-projection array skin patch (nanopatchTM) as an alternate delivery system to intramuscular injection for delivering an alum adjuvanted human papillomavirus (hpv) vaccine (gardasil®) commonly used as a prophylactic vaccine against cervical cancer. methodology/principal findings: micro-projection arrays dry-coated with vaccine material (gardasil®) delivered to c57bl/6 mouse ear skin released vaccine within 5 minutes. to assess vaccine immunogenicity, doses of corresponding to hpv-16 component of the vaccine between 0.43±0.084 ng and 300±120 ng (mean ± sd) were administered to mice at day 0 and day 14. a dose of 55±6.0 ng delivered intracutaneously by micro-projection array was sufficient to produce a maximal virus neutralizing serum antibody response

at day 28 post vaccination. neutralizing antibody titres were sustained out to 16 weeks post vaccination, and, for comparable doses of vaccine, somewhat higher titres were observed with intracutaneous patch delivery than with intramuscular delivery with the needle and syringe at this time point. conclusions/significance: use of dry micro-projection arrays (nanopatchTM) has the potential to overcome the need for a vaccine cold chain for common vaccines currently delivered by needle and syringe, and to reduce risk of needle-stick injury and vaccine avoidance due to the fear of the needle especially among children. © 2010 corbett et al."
Hegarty, C., McConville, A., McGlynn, R. J., Mariotti, D., & Davis, J.. (2019). Design of composite microneedle sensor systems for the measurement of transdermal pH. Materials Chemistry and Physics

Plain numerical DOI: 10.1016/j.matchemphys.2019.01.052
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"Carbon loaded polystyrene microneedle patches have been prepared using silicone micro-moulding techniques and the ability of the needles to serve as viable transdermal sensors has been evaluated. the population of quinone groups at the interface of the embedded carbon nanoparticles was increased through anodisation and their ph dependent redox transitions exploited as the basis of a reagentless ph sensor. the peak position of the quinone oxidation process was found to shift in accordance with nernstian behaviour and the influence of penetration depth on response has been investigated. the analytical applicability of the microneedle electrode patch was critically evaluated through using tomato skin as model transdermal skin mimic. despite the increased complexity of the matrix, the microneedle sensor response was found to compare favourably with conventional/commercial ph probes."
Li, W., Tang, J., Terry, R. N., Li, S., Brunie, A., Callahan, R. L., … Prausnitz, M. R.. (2019). H E A L T H A N D M E D I C I N E Long-acting reversible contraception by effervescent microneedle patch. Sci. Adv

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"To increase access to long-acting contraception, we developed a reversible contraceptive microneedle patch that is simple-to-administer, slowly releases contraceptive hormone (levonorgestrel) for >1 month, and generates no biohazardous sharps waste. after manually pressing the patch to skin for 1 min, microneedles rapidly separate from the patch within the skin due to effervescence triggered by contact with skin's interstitial fluid, as demonstrated in rats and human participants. long-acting contraception is achieved by formulating microneedles with a biodegradable polymer [poly(lactic-co-glycolic) acid] that slowly releases levonorgestrel for ~1 month in vitro. in rats, the patch maintained levonorgestrel concentration above the human contraceptive threshold level for >1 month, and a placebo micro needle patch was well-tolerated in human participants. women of reproductive age in three continents demonstrated interest in and preference for long-acting contraception by microneedle patch. these studies indicate that an effervescent microneedle patch could facilitate greater access to long-acting contraception."
Kesarwani, A., Yadav, A. K., Singh, S., Gautam, H., Singh, H. N., Sharma, A., & Yadav, C.. (2013). An Official Publication of Association of Pharmacy Professionals T HEORETICAL ASPECTS OF T RANSDERMAL D RUG D ELIVERY S YSTEM. Bulletin of Pharmaceutical Research

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“Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver the drug through the skin in order to achieve systemic absorption of drug at a predetermined rate over a prolonged period of time. its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. there are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. due to technological advancement, many new techniques which have attained attention are iontophoresis, phonophoresis, electroporation micro needles etc. different types of transdermal patches can be prepared by varying methods. transdermal patches can be evaluated by interaction studies, folding endurance, thickness of the patch, weight uniformity, drug content and i n v i tr o studies. this review covers general aspects like advantages, methods of preparation of transdermal patches, evaluation, basic components of transdermal drug delivery system.”
Desale Rohan, S., Wagh Kalpesh, S., Akarte Anup, M., Baviskar Dheeraj, T., & Jain Dinesh, K.. (2012). Microneedle technology for advanced drug delivery: A review. International Journal of PharmTech Research

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“The objective of this review article is to summarize recent data, description results and basic functionality of silicon microneedles array through biodegradable instructions. in order to avoid the main troubles related to drug degradation by gastrointestinal track and their elimination through the liver, an easy solution can be fabrication of microneedles array with biodegradable instructions. transdermal drug delivery can avoid drug degradation, and it has a low diffusion coefficient so it is complicated to transport hydrophilic and high molecular weight drug (>500da) using passive patches. while, there is about 20 species of drug that relevant to former patches. micro-needle can convey hydrophilic and molecular weight, because it have valuable source of intellectual property. there are many studies in transdermal drug delivery, blood extraction, skin care fields with a micro-needle. existing micro-needle through using silicon, metal, and polymer materials. to make 3-d shape micro-needle mold, inclined uv lithography is used, but this process is complicated to control process condition and its process output ratio is so low. this review suggests the novel process using dicing progression with an inclined sharp edge to make the sharp shape of microneedle information. and the optical assessment module is made for evaluating the drug delivering ratio according to the needle length and insertion times. this estimation module has a water chamber and membrane to copy the drug delivery mechanism. we can discover that the drug delivering ratio can enlarge when use a longer needle as the surface area with drug sticking can be augmented.”
Hegarty, C., McKillop, S., McGlynn, R. J., Smith, R. B., Mathur, A., & Davis, J.. (2019). Microneedle array sensors based on carbon nanoparticle composites: interfacial chemistry and electroanalytical properties. Journal of Materials Science

Plain numerical DOI: 10.1007/s10853-019-03642-1
DOI URL
directSciHub download

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“Conductive microneedle patches consisting of carbon nanoparticles embedded in a polystyrene matrix have been prepared using micro-moulding techniques. the interfacial properties of the structures before and after electrochemical etching have been characterised using x-ray photoelectron spectroscopy and contact angle. anodisation of the needles leads to a significant increase in oxygen functionality and is shown to dramatically improve the electroanalytical capabilities of the microneedle array. the detection of uric acid in horse blood was used as a model system through which to assess the performance of the system. the composite approach is shown to lead to viable carbon-based sensors and can offer a rapid prototype option for the development of tailored microneedle systems.”
Gardeniers, H. J. G. E., Luttge, R., Berenschot, E. J. W., De Boer, M. J., Yeshurun, S. Y., Hefetz, M., … Van Den Berg, A.. (2003). Silicon micromachined hollow microneedles for transdermal liquid transport. Journal of Microelectromechanical Systems

Plain numerical DOI: 10.1109/JMEMS.2003.820293
DOI URL
directSciHub download

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“This paper presents a novel process for the fabrication of out-of-plane hollow micro needles in silicon. the fabrication method consists of a sequence of deep-reactive ion etching (drie), anisotropic wet etching and conformal thin film deposition, and allows needle shapes with different, lithography-defined tip curvature. in this study, the length of the needles varied between 150 and 350 micrometers. the widest dimension of the needle at its base was 250 ?m. preliminary application tests of the needle arrays show that they are robust and permit skin penetration without breakage. transdermal water loss measurements before and after microneedle skin penetration are reported. drug delivery is increased approximately by a factor of 750 in microneedle patch applications with respect to diffusion alone. the feasibility of using the microneedle array as a blood sampler on a capillary electrophoresis chip is demonstrated.”
Dardano, P., Caliò, A., Politi, J., Rea, I., Rendina, I., & De Stefano, L.. (2016). Optically monitored drug delivery patch based on porous silicon and polymer microneedles. Biomedical Optics Express

Plain numerical DOI: 10.1364/boe.7.001645
DOI URL
directSciHub download

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“© 2016 optical society of america. fabrication and characterization of an optically monitored hybrid patch for local administration of drugs, based on polymeric micro-needles and a porous silicon free-standing membrane, are reported. the microneedles are realized by an innovative photolithographic approach that allows fine tuning of geometrical parameters, using polyethylene glycol and a commercial photo-catalyzer. the porous silicon multilayer not only increases the storage of a relevant amount of the drug, but also offers a continuous, naked-eye monitoring of the drug delivery process. as a proofof- concept experiment, we report our results on the release of a dye molecule (fluorescein, 332

da) in a phosphate saline buffer."
Tang, Y. H., Lin, Y. H., Huang, T. T., Wang, J. S., Hu, Y. C., & Shiao, M. H.. (2019). Development of micro-needle array for Tumor vaccine patch applications. In Proceedings of the IEEE Conference on Nanotechnology

Plain numerical DOI: 10.1109/NANO46743.2019.8993929
DOI URL
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"Microneedles have been given sufficient potential as a patch for transdermal drug delivery. however, very few product on the application of mems for the vaccine delivery is reported. the aim of this paper is to develop the vaccine coated solid microneedle patch by the use of micro-electromechanical systems (mems) technology, the fabrication of a silicon microneedle arrays made by uv lithography, inductively coupled plasma reactive ion etching (icp-rie) and wet chemical etching process. to solve the limitation of low vaccine volume carried, groove and pocket structure will be introduced. besides, through the control of formulation of surface tension, viscosity and hydrophilic/ hydrophobic properties by optimization of vaccine formulation composition, the vaccine carried volume can be achieved. moreover, bioactive of vaccine will be investigated by parameter of the osmotic pressure and phase-transformation. combination of vaccine formulation and microneedle to fabricate the delivery device, the release profile of the device will be evaluated in vitro, and will be further evaluated in the artificial human skin system to observe the immune response. the research will be included two parts: 1. vaccine coated solid microneedle patch device will be established; 2. design a microneedle patch having specific application, such as enterovirus 71 vaccines, and to realize a commercial available vaccine microneedle patch device. consequently, a microneedle array with biodegradable porous tips was further developed based on the fabricated microneedles patch."
Lee, H., Jeon, H. Y., Park, S., Lee, H.-W., & Sungmin, B.. (2011). Micro needle array fabrication for drug delivery and drug delivery evaluation test using optical inspection module. International Conference on Nanotechnology and Biosensors

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"For drug delivery into the body, oral medication is primarily problematic due to drug degradation in the gastrointestinal tract and elimination through the liver. this method delivers a drug into a body at once and absorbed, so drug concentration in plasma increased rapidly and reaching the apex. then drug concentration is decreased gradually according to the body's metabolism. this drug concentration profile shows that if drug concentration over the maximum desired level, it can give bad effect to the body and below the minimum desired level, it is difficult to expect drug effect. effective drug delivery profile is constant delivery of relevant drug concentration it can maintain plasma's drug concentration. transdermal drug delivery can prevent drug degradation, and it can control release. stratum corneum (the outer layer of skin) is a major barrier for drug delivery, it has a low diffusion coefficient so it is difficult to transport hydrophilic and high molecular weight drug (>500da) using passive patches. since, there is about 20 species of drug that applicable to former patches. micro-needle can deliver hydrophilic and molecular weight, because it made micro scale holes in the skin. there are many studies in transdermal drug delivery, blood extraction, skin care fields using a micro-needle. existing micro-needle made using silicon, metal, polymer materials. to make 3-d shape micro-needle mold,

inclined uv lithography is used, but this process is difficult to control process condition and its process output ratio is so low. this research suggests the novel process using dicing process with an inclined sharp edge to make the sharp shape of a micro- needle tips. and the optical inspection module is made for evaluating the drug delivering ratio according to the needle length and insertion times. this evaluation module has a water chamber and membrane to copy the drug delivery mechanism. we can find that the drug delivering ratio can increase when use a longer needle because the surface area with drug sticking can be increased”
Nguyen, T. T., Nguyen, T. T. D., Tran, N. M. A., & Vo, G. Van. (2022). Advances of microneedles in hormone delivery. Biomedicine and Pharmacotherapy

Plain numerical DOI: 10.1016/j.biopha.2021.112393
DOI URL
directSciHub download

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“The skin is recognized as a potential target for local and systemic drug delivery and hormone. however, the transdermal route of drug administration seems to be limited by substantial barrier properties of the skin. recently, delivering hormone via the skin by transdermal patches is a big challenge because of the presence of the stratum corneum that prevents the application of hormone via this route. in order to overcome the limitations, microneedle (mn), consisting of micro-sized needles, are a promising approach to drill the stratum corneum and release hormone into the dermis via a minimal-invasive route. this review aimed to highlight advances in research on the development of mns-based therapeutics for their implications in hormone delivery. the challenges during clinical translation of mns from bench to bedside are also discussed.”
Ahn, B.. (2020). Optimal Microneedle Design for Drug Delivery Based on Insertion Force Experiments with Variable Geometry. International Journal of Control, Automation and Systems

Plain numerical DOI: 10.1007/s12555-019-0220-8
DOI URL
directSciHub download

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“Microneedles, which prick micro holes in the stratum corneum (sc), are promising minimally invasive drug delivery devices alternating pills, conventional needles, or transdermal patches. however, the microneedle fabrication based on the optimal design has been studied rarely. in this paper, the forces required to insert microneedles into a skin model were measured over the various geometries in order to optimize the microneedle design. to measure the insertion force, the microneedles were fabricated with inclined uv lithography and hot embossing processes. the insertion force was measured with a custom-made dynamic displacement device which can measure and record the force of mn range loads. the insertion force is strongly related with tip angle and radius of tip’s curvature. the insertion forces increase with increasing width of shaft, but the relation is very week and the radius of fillet in the experimental range has no influence on the insertion force. this result can be used as an optimal design guide on the geometries of microneedle.”
Hu, H. W., Yi-Chun, D., & Ming-Jui, W.. (2019). FP555Multiple alert threshold of blood leakage detector in hemodialysis to increase the economic benefits of care

. Nephrology Dialysis Transplantation

Plain numerical DOI: 10.1093/ndt/gfz106.fp555
DOI URL
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“INTRODUCTION: a puncture from body surface is commonly used in clinical treatment, such as hemodialysis or central venous catheters. needle dislodgement associated with higher leakage or risk of infection, although the probability is low, it can be fatal. at present, many existing leak detection devices have been used, but most of them have a single point and just determine whether there is blood leakage. it is impossible to accurately determine the difference of liquid leakage, and many micro-leakage causes trouble to the nursing staff.it increases the cumbersome nursing work. our team designed the patch which can sense the amount of liquid according to the area of blood leakage, and effectively classify the warning into micro-leakage and severe blood leakage. after the determination, different care modes can be provided. method(s): we designed a leak-sensing patch. by multi-channel circuit design and soft board process, we can determine the severity of the leak by sensing the amount of liquid absorbed by the patch to detect different impedance values. using a fake hand simulation experiment, different amounts of liquid wet the patch and confirm the distribution of blood leakage of 0.1 ml-1.5ml. we can set the customization threshold to reduce the gauze replacement cost and the burden of nursing staff, and also reach the warning effect nursing staff. result(s): a leak detection patch has been designed. after the prosthesis simulation experiment, a threshold can be set freely every 0.1-0.2 ml, and different levels of warnings can be designed according to the customized clinical requirements. it reduces the burden of nursing staff to achieve the effect of segmentation warning. conclusion(s): the research team developed a multi-threshold sensing patch that can determine the serious blood leak and slight blood leak, and provide accurate judgment of the nursing staff’s blood leakage care to achieve economic cost effectiveness.”
Dalvi, M., Kharat, P., Thakor, P., Bhavana, V., Singh, S. B., & Mehra, N. K.. (2021). Panorama of dissolving microneedles for transdermal drug delivery. Life Sciences

Plain numerical DOI: 10.1016/j.lfs.2021.119877
DOI URL
directSciHub download

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“Recently, microfabrication technology has been developed to increase the permeability of drugs for transdermal delivery. microneedles are ultra-small needles usually in the micron size range (different dimensions in micron), generate pores, and allow for delivery of local medication in the systemic circulation via skin. the microneedles have been available in dissolving, solid, coated, hollow, and hydrogel-based microneedles. dissolving microneedles have been fabricated using micro-molding, photo-polymerization, drawing lithography and droplet blowing techniques. dissolving microneedles could be a valuable option for the delivery of low molecular weight drugs, peptides, enzymes, vaccines and bio-therapeutics. it consists of water-soluble materials including maltose, polyvinyl pyrrolidone, chondroitin sulfate, dextran, hyaluronic acid, and albumin. the microneedles have almost dissolved after patch removal, leaving only blunt stubs behind, which are easily removable. in this review, we

summarize the major building blocks, classification, fabrication techniques, characterization, diffusion models and application of microneedles in diverse area. we also reviewed the regulatory aspects, computational studies, patents, clinical data, and market trends of microneedles."
Yan, Q., Weng, J., Shen, S., Wang, Y., Fang, M., Zheng, G., … Yang, G.. (2021). Finite element analysis for biodegradable dissolving microneedle materials on skin puncture and mechanical performance evaluation. Polymers

Plain numerical DOI: 10.3390/polym13183043
DOI URL
directSciHub download

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"In this study, a micro-molding technology was used to prepare the microneedles (mns), while a texture analyzer was used to measure its young's modulus, poisson's ratio and compression breaking force, to evaluate whether the mns can penetrate the skin. the effects of different materials were characterized by their ability to withstand stresses using the structural mechanics module of comsol multiphysics. carboxymethylcellulose (cmc) was chosen as the needle formulation material with varying quantities of polyvinyl pyrrolidone (pvp), polyvinyl alcohol (pva) and hyaluronic acid (ha) to adjust the viscosity, brittleness, hardness and solubility of the material. the results of both the experimental tests and the predictions indicated that the hardest tip material had a solids content of 15% (w/w) with a 1:2 (w/w) cmc: ha ratio. furthermore, it was shown that a solid content of 10% (w/w) with a 1:5 (w/w) cmc: pva ratio is suitable for making patches. the correlation between the mechanical properties and the different materials was found using the simulation analysis as well as the force required for different dissolving microneedles (dmns) to penetrate the skin, which significantly promoted the research progress of microneedle transdermal drug delivery."
Gala, R. P., Uz Zaman, R., D'souza, M. J., & Zughaier, S. M.. (2018). Novel whole-cell inactivated Neisseria gonorrhoeae microparticles as vaccine formulation in microneedle-based transdermal immunization. Vaccines

Plain numerical DOI: 10.3390/vaccines6030060
DOI URL
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"Neisseria gonorrhoeae is a strict human pathogen responsible for more than 100 million new sexually transmitted infections worldwide each year. due to the global emergence of antibiotic resistance, the center for disease control (cdc) recently listed n. gonorrhoeae as an urgent threat to public health. no vaccine is available in spite of the huge disease burden and the possibility of untreatable gonorrhea. the aim of this study is to investigate the immunogenicity of a novel whole-cell-based inactivated gonococcal microparticle vaccine formulation loaded in dissolvable microneedles for transdermal administration. the nanotechnology-based vaccine formulation consists of inactivated whole-cell gonococci strain cdc-f62, spray dried and encapsulated into biodegradable cross-linked albumin matrix with sustained slow antigen release. the dry vaccine nanoparticles were then loaded in a dissolvable microneedle skin patch for transdermal delivery. the efficacy of the whole-cell microparticles vaccine formulation loaded in microneedles was assessed in vitro using dendritic cells and macrophages as

well as in vivo mouse model. antibody titers were measured using an enzyme immunosorbent assay (elisa) and antigen-specific t lymphocytes were assessed in spleens and lymph nodes. here we report that whole-cell-based gonococcal microparticle vaccine loaded in dissolvable microneedles for transdermal administration induced significant increase in antigen-specific igg antibody titers and antigen-specific cd4 and cd8 t lymphocytes in mice compared to gonococcal antigens in solution or empty microneedles. significant increase in antigen-specific igg antibody levels was observed at the end of week 2 in groups that received the vaccine compared to the group receiving empty nanoparticles. the advantages of using formalin-fixed whole-cell gonococci that all immunogenic epitopes are covered and preserved from degradation. the spherical shaped micro and nanoparticles are biological mimics of gonococci, therefore present to the immune system as invaders but without the ability to suppress adaptive immunity. in conclusion, the transdermal delivery of microparticles vaccine via a microneedle patch was shown to be an effective system for vaccine delivery. the novel gonorrhea nanovaccine is cheap to produce in a stable dry powder and can be delivered in microneedle skin patch obviating the need for needle use or the cold chain."
Bozorgi, A., & Fahimnia, B.. (2021). Micro array patch (MAP) for the delivery of thermostable vaccines in Australia: A cost/benefit analysis. Vaccine

Plain numerical DOI: 10.1016/j.vaccine.2021.08.016
DOI URL
directSciHub download

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"Background: it is anticipated that transforming the vaccine supply chain from syringe-and-needle to thermostable vaccines enabled by micro array patch (map) will result in reduced supply chain costs as well as reduced wastes (environmental impact) and improved safety. this paper provides a thorough cost comparison of the conventional syringe-and-needle vaccine supply chain versus the map vaccine supply chain for influenza vaccine delivery in australia. objective: to determine the potential cost implications and general benefits of replacing syringe-and-needle flu vaccine with map-enabled thermostable flu vaccine in australia. methods: we first provide a snapshot of the existing flu vaccine supply chain in australia including its limitations and opportunities for improvement. data/information is collected through interviewing the key stakeholders across vaccine supply chain including vaccine manufacturers, logistics providers, clinics, hospitals, and pharmacies. a cost/benefit analysis of the anticipated supply chain of the map-enabled vaccine will reveal the opportunities and challenges of supply chain transformation for flu vaccine delivery in australia. findings: our high-level practice-informed cost/benefit analysis identifies cold chain removal as an important source of cost saving, but administrative cost savings appear to be even more significant (e.g., time saving for nurses and those involved in cold chain management). our analysis also identifies the key benefits and limitations of vaccine supply chain transformation in australia. conclusion: we conclude that the benefits of moving from syringe-and-needle vaccines to thermostable map-delivered vaccines are beyond transportation and storage cost saving. potential benefits through cost saving, waste reduction, and service level improvement are discussed along with various safety and wellbeing consequences as well as directions for future research in this area."
Koester, P. J., Tautorat, C., Beikirch, H., Gimsa, J., & Baumann, W.. (2010). Recording electric potentials from single adherent cells with 3D microelectrode arrays after local electroporation. Biosensors and Bioelectronics

Plain numerical DOI: 10.1016/j.bios.2010.08.003
DOI URL
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“This short communication reports on the innovative method of the local micro-invasive needle electroporation (lomine) of single adherent cells. the investigation of cellular reactions in living cell cultures represents a fundamental method, e.g. for drug development and environmental monitoring. existing classical methods for intracellular measurements using, e.g. patch clamp techniques are time-consuming and complex. present patch-on-chip systems are limited to the investigation of single cells in suspension. nevertheless, the most part of the cells of the human body is adherently growing. therefore, we develop a new chip system for the growth of adherent cells with 64 micro-structured needle electrodes as well as 128 dielectrophoretic electrodes, located within a measuring area of 1mm2. with this analytical chip, the intracellular investigation of electro-chemical changes and processes in adherently growing cells will become possible in the near future. here, we present first intracellular measurements with this chip system. © 2010 elsevier b.v.”
Nandedkar, T. D.. (2009). Nanovaccines: Recent developments in vaccination. Journal of Biosciences

Plain numerical DOI: 10.1007/s12038-009-0114-3
DOI URL
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“In the past 100 years, vaccination has contributed immensely to public health by preventing a number of infectious diseases. attenuated, killed or part of the microorganism is employed to stimulate the immune system against it. progress in biotechnology has provided protective immunity through dna vaccines. in recent years, nanovaccine is a novel approach to the methodology of vaccination. nanomaterials are delivered in the form of microspheres, nano-beads or micro-nanoprojections. painless, effective and safe needle-free routes such as the intranasal or the oral route, or patches of microprojections to the skin are some of the approaches which are in the experimental stage at present but may have a great future ahead in nanovaccination. © indian academy of sciences.”
Bozorgi, A., & Fahimnia, B.. (2021). Transforming the vaccine supply chain in Australia: Opportunities and challenges. Vaccine

Plain numerical DOI: 10.1016/j.vaccine.2021.08.033
DOI URL
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“Background: analyzing potential benefits of thermostable vaccines delivered through micro array patch (map) has received great attention in low and middle-income countries. the experience may or may not be the same in developed countries where the infrastructure is more developed. it is anticipated that transforming the vaccine supply chain from syringe-and-needle to thermostable map-

delivered vaccines will result in reduced supply chain costs – including manufacturing/supply, logistics/distribution, and administration costs – as well as reduced wastes and improved safety. this paper provides an end-to-end supply chain analysis comparing the key aspects (cost, safety and environmental aspects) of the conventional syringe-and-needle vaccine supply chain with those of the map vaccine supply chain for influenza vaccine delivery in australia. directions for future research in this area will be provided. objective: to determine the potential supply chain impacts of replacing syringe-and-needle flu vaccine with map-enabled thermostable flu vaccine in australia. methods: we analyze the current flu vaccine supply chain in australia to identify practical limitations and opportunities for improvement. data/information is collected through interviewing the key stakeholders across vaccine supply chain including vaccine manufacturers, logistics providers, clinics, hospitals, and pharmacies. findings: a detailed practice-informed analysis is completed on the key operations of the flu vaccine supply chain. barriers and limitations of the conventional flu vaccine are discussed, along with potential improvements that can be achieved through the implementation of map-enabled flu vaccine delivery. we discuss how technology-driven innovations can help advance vaccine supply chains, improve vaccine visibility, reduce wastes, and enable informed decision-making. conclusion: we find that the benefits of moving from syringe-and-needle vaccines to thermostable map-delivered vaccines are beyond transportation and storage cost saving. potential benefits through cost saving, waste reduction, and service level improvement are discussed along with various safety and wellbeing consequences followed by directions for future research in this area."
Yang, Y. C., Lin, Y. T., Yu, J., Chang, H. T., Lu, T. Y., Huang, T. Y., … Lin, T. E.. (2021). MXene Nanosheet-Based Microneedles for Monitoring Muscle Contraction and Electrostimulation Treatment. ACS Applied Nano Materials

Plain numerical DOI: 10.1021/acsanm.1c01237
DOI URL
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"MXenes belong to a large family of two-dimensional layered transition-metal carbides and nitrides. mxene nanosheets integrate the fascinating advantages of high electronic conductivity, excellent biocompatibility, and acid/base resistance. herein, we demonstrate a 'hospital-on-a-chip'system with multifunctional microneedle electrodes for biosensing and electrostimulation using highly stable mxene nanosheets. this system consists of integrated microchip biosensors for an efficient diagnosis and medical treatment elements for therapies, thus resembling a miniaturized hospital. microneedles are composed of dozens of micron-sized needles that can be used as an effective and painless transdermal patch to puncture the dead skin barrier for drug delivery or biosensing purposes since they are directly in contact with the dermal layer inside the human body. the wearable mxene nanosheet-based microneedles can sense the tiny electric potential difference generated from the human eye movements or muscle contraction from the human arm. therefore, the diseases associated with neuromuscular abnormalities such as myasthenia gravis can be monitored. consequently, the transcutaneous electrical nerve stimulation treatment can be applied according to the feedback of the micro-biosensors. in addition, mxene microneedles can offer an electrically controlled drug delivery platform and the function of enhancing blood coagulation. finally, mxene nanosheet-based microneedles provide an interesting platform for wearable micro-biosensors and offer an essential part of the hospital-on-a-chip system."
Chen, G., Hao, B., Ju, D., Liu, M., Zhao, H., Du, Z., & Xia, J.. (2015). Pharmacokinetic and pharmacodynamic study of triptolide-loaded liposome hydrogel patch under microneedles on rats with collagen-induced arthritis

. Acta Pharmaceutica Sinica B

Plain numerical DOI: 10.1016/j.apsb.2015.09.006
DOI URL
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“Triptolide (tp), a major active component of tripterygium wilfordii hook.f. (twhf), is used to treat rheumatoid arthritis (ra). however, it has a narrow therapeutic window due to its serious toxicities. to increase the therapeutic index, a new triptolide-loaded transdermal delivery system, named triptolide-loaded liposome hydrogel patch (tp-lhp), has been developed. in this paper, we used a micro-needle array to deliver tp-lhp to promote transdermal absorption and evaluated this treatment on the pharmacokinetics and pharmacodynamics of tp-lhp in a rat model of collagen-induced arthritis (cia). the pharmacokinetic results showed that transdermal delivery of microneedle tp-lhp yielded plasma drug levels which fit a one-compartment open model. the relationship equation between plasma concentration and time was c=303.59×(e-0.064t-e-0.287t). the results of pharmacodynamic study demonstrated that tp-lhp treatment mitigated the degree of joint swelling and suppressed the expressions of fetal liver kinase-1, fetal liver tyrosine kinase-4 and hypoxia-inducible factor-1? in synovium. other indicators were also reduced by tp-lhp, including hyperfunction of immune, interleukin-1? and interleukin-6 levels in serum. the therapeutic mechanism of tp-lhp might be regulation of the balance between th1 and th2, as well as inhibition of the expression and biological effects of vascular endothelial growth factor.”
Yadav, J. D., Vaidya, K. A., Kulkarni, P. R., & Raut, R. A.. (2011). Microneedles: Promising technique for transdermal drug delivery. International Journal of Pharma and Bio Sciences

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“Transdermal drug delivery using microneedle is a novel method of drug delivery. microneedle is like conventional needles only fabricated in micro scale. the advantage of using microneedle is that it does not pass the stratum corneum. the dosing in microgram quantities can be done by this type of needle. the mechanism of action is based on temporary mechanical disruption of skin. the drug, in the form of biomolecules, is encapsulated within the microneedles, which are then inserted into the skin in the same way a drug like nitroglycerine is released into the bloodstream from a patch. the needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. the review covers the various methods of drug delivery like poke with patch approach, coat and poke approach, biodegradable microneedles, hollow microneedles and dip and scrape. the various method of preparation of microneedles include molding, casting, laser cutting. the in vivo safety assessment and the evaluation of microneedle have shown that this technique can be used safely. there are various advantages of the microneedle trans dermal drug delivery methods over other techniques which helps to make it successful delivery system.”
Takai, K., & Taniguchi, M.. (2017). Targeted Epidural Blood Patch Under O-Arm–Guided Stereotactic Navigation in Patients with Intracranial Hypotension Associated with a Spinal Cerebrospinal Fluid Leak and Ventral Dural Defect. World Neurosurgery

Plain numerical DOI: 10.1016/j.wneu.2017.07.168

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“Objective targeted epidural blood patch (ebp) at the site of a presumed cerebrospinal fluid leak reportedly has better outcomes than non-targeted ebp; however, it is associated with a higher risk of wrong-site injection, such as iatrogenic subarachnoid or intramuscular injections, which lead to reintervention because of the insufficient coverage of injected blood. methods eight patients with intracranial hypotension owing to a csf leak diagnosed with myelographic computed tomography (ct) and thin-cut magnetic resonance imaging (mri) received an epidural blood patch under o-arm–guided stereotactic navigation. results the leak site was identified on the basis of myelographic ct findings of a micro-spur, epidural contrast medium extravasations, and mri findings of a ventral dural defect. during the ebp procedure, no iatrogenic dural puncture or subarachnoid injection occurred because o-arm–guided stereotactic navigation provided real-time feedback on the needle trajectory. o-arm ct revealed the sufficient coverage of injected blood following the first injection in 6 of 8 patients. in the 2 remaining patients, a second injection was performed during the same session because of insufficient coverage at the previous site. in all patients, complete recovery from orthostatic headaches was achieved after a single session. conclusions o-arm–guided navigation facilitated ebp by enabling real-time observations of the needle trajectory and distribution of injected blood while simultaneously avoiding major complications, such as wrong-site injections or reintervention.”
Söbbeler, F. J., & Kästner, S. B.. (2018). Effects of transdermal lidocaine or lidocaine with prilocaine or tetracaine on mechanical superficial sensation and nociceptive thermal thresholds in horses. Veterinary Anaesthesia and Analgesia

Plain numerical DOI: 10.1016/j.vaa.2017.10.003
DOI URL
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“Objective: to evaluate the transdermal local anaesthetic effect of lidocaine or lidocaine combined with prilocaine or tetracaine in horses. study design: experimental, randomized study. animals: a total of five healthy adult warmblood horses. methods: horses were clipped bilaterally at the withers, cranial saddle area and caudal saddle area. baseline measurements for mechanical superficial sensation via von frey filaments and nociceptive thermal thresholds were performed. a 5% lidocaine patch (12 hour exposure, treatment l), a lidocaine/prilocaine cream (each 2.5%, treatment lp) and a lidocaine/tetracaine cream (each 7%, treatment lt) were applied (both 2 hour exposure). the same product was applied at the same location bilaterally, but on the right side an epidermal micro-perforation (dermaroller, 1200 needles) was performed prior to application. a total of five more measurements were performed at each location, immediately at the end of exposure time followed by hourly measurements. thermal thresholds normalized to thermal excursion were analysed. one- or two-way anova and the wilcoxon signed-rank test were used for statistical analysis with $p < 0.05$ considered significant. results: epidermal micro-perforation had no enhancing effect. treatments l, lp, and lt resulted in increased thermal excursion (%) immediately (84.7 ± 12.9; 100.0 ± 0.0; 100.0 ± 0.0) and 1 hour (81.7 ± 66; 86.0 ± 17.7; 87.7 ± 14.4) after the removal of the respective product compared to baseline (66.1 ± 9.3; 69.9

± 8.3; 76.5 ± 7.8). superficial mechanical sensation was decreased by the lidocaine-and-tetracaine cream at all time points, and by the lidocaine patch and lidocaine-and-prilocaine cream for three measurements. conclusions and clinical relevance: eutectic mixtures of lidocaine with either prilocaine or tetracaine led to a reduction in thermal nociception and mechanical sensation for up to 2 hours."
Han, Z., Zeng, R., Zhou, P., Yang, L., Ren, Y., & Qu, Y.. (2021). Preparation and preliminary evaluation of insulin-loaded Bletilla striata polysaccharide dissolving microneedles with flexible patches . Chinese Traditional and Herbal Drugs

Plain numerical DOI: 10.7501/j.issn.0253-2670.2021.07.007
DOI URL
directSciHub download

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"Objective: the insulin (ins)-loaded dissolving microneedles with flexible patches (ins-dmns) was prepared by bletilla striata polysaccharide (bsp) and polyvinyl alcohol (pva) for the first time, the physicochemical properties and transdermal delivery performance of ins-dmns were preliminarily evaluated. methods: ins-dmns were prepared by micro-molding technique. the concentration of bsp and pva was investigated with the hardness of needle bodies, flexibility of patches and formability of microneedles as the evaluation index. the morphological characteristics was observed by scanning electron microscopy. drug loading, solubility, skin irritation, mechanical strength and stability were tested. the transdermal release and diffusion of ins were observed by confocal microscopy. in vitro transdermal performance of ins-dmns was investigated by franz diffusion cell, and in vivo pharmacodynamics were studied to investigate their hypoglycemic effect on diabetic rats. results: the prepared ins-dmns were pyramidal in shape with uniform needle bodies and excellent mechanical strength. meanwhile, the needle bodies of ins-dmns could dissolve in 2 h, and the patches were flexible and flat. the dosage of ins was (0.25 ± 0.02) iu per patch, and the skin damage induced by ins-dmns was slight and recovered quickly. the stability was excellent and ins could reach 220 ?m inside the skin. moreover, in vitro skin penetration results showed that the cumulative penetration of ins in ins-dmns reached 89.63% after 12 h, which proved that the bletilla striata polysaccharide dissolving microneedles with flexible patches could effectively improve the transdermal penetration of ins. the results of in vivo pharmacodynamics showed that ins-dmns exhibited a significant hypoglycemic effect, and compared with subcutaneous administration, microneedle administration was more sustainable. conclusion: ins-dmns realized the transdermal delivery of ins, where the needle bodies were mechanically robust enough to insert into the skin and continuously release drugs, while the flexible patches provided better skin adhesion."
Friedmann, A., Cismak, A., Tautorat, C., Koester, P. J., Baumann, W., Held, J., … Heilmann, A.. (2012). FIB preparation and SEM investigations for three-dimensional analysis of cell cultures on microneedle arrays. Scanning

Plain numerical DOI: 10.1002/sca.20297
DOI URL
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"We report the investigation of the interfaces between microneedle arrays and cell cultures in patch-on-

chip systems by using focused ion beam (fib) preparation and scanning electron microscopy (sem). first, fib preparations of micro chips are made to determine the size and shape of the designed microneedles. in this essay, we investigate the cell-substrate interaction, especially the cell adhesion, and the microneedle's potential cell penetration. for this purpose, cross-sectional preparation of these hard/soft hybrid structures is performed by the fib technology. by applying the fib technology followed by high-resolution imaging with sem, new insights into the cell-substrate interface can be received. one can clearly distinguish between cells that are only in contact with microneedles and cells that are penetrated by microneedles. a stack of slice images is collected by the application of the slice-and-view setup during fib preparation and is used for threedimensional reconstruction of cells and micro-needles. © 2011 wiley periodicals, inc."
Soltani-Arabshahi, R., Wong, J. W., Duffy, K. L., & Powell, D. L.. (2014). Facial allergic granulomatous reaction and systemic hypersensitivity associated with microneedle therapy for skin rejuvenation. JAMA Dermatology

Plain numerical DOI: 10.1001/jamadermatol.2013.6955
DOI URL
directSciHub download

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"IMPORTANCE microneedle therapy includes skin puncture with multiple micro-sized needles to promote skin rejuvenation or increase transdermal delivery of topical medications. in cosmetic practices, various cosmeceuticals are applied before microneedling to enhance the therapeutic effects. this results in intradermal tattooing of the topical product. despite rapid increase in the use of microneedles in dermatology, there are few data about their safety. observations we describe 3 women, aged 40s to 60s, who developed facial granulomas following microneedle therapy for skin rejuvenation. two patients had undergone microinjection of the same branded topical moisturizer (vita c serum; sanítas skincare) during microneedle therapy. biopsy in all cases showed foreign body-type granulomas. results of tissue cultures were negative. chest radiography and serum angiotensinconverting enzyme findings were normal. the first 2 patients had a positive patch test reaction to vita c serum. initial treatment with topical and oral corticosteroids was ineffective. therapy with doxycycline hydrochloride and minocycline hydrochloride led to partial improvement in one case and resolution in another. conclusions and relevance application of topical products prior to microneedling can introduce immunogenic particles into the dermis and potentiate local or systemic hypersensitivity reactions. because the microneedle therapy system is accessible for home use, health care providers need to be aware of its potential consequences. copyright 2014 american medical association. all rights reserved."
Desale, R. S., Wagh, K. S., Akarte, A. M., Baviskar, D. T., & Jain, D. K.. (2012). Microneedle Technology for Advanced Drug Delivery : A Review. International Journal of PharmTech Research

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"Th e o bj e c ti v e o f t h i s r e v i e w a r t i c l e i s t o s um m a r i z e re c e n t d a t a , d e s c r i p ti o n re s u l t s a n d b a s i c functionality of silicon microneedles array through biodegradable instructions. in order to avoid the main troubles related to drug degradation by gastrointestinal track and their elimination through the liver, an easy solution can be fabrication of microneedles array with biodegradable instructions. transdermal drug delivery can avoid drug degradation, and it has a low

diffusion coefficient so it is complicated to transport hydrophilic and high molecular weight drug (>500da) using passive patches. while, there is about 20 species of drug that relevant to former patches. micro-needle can convey hydrophilic and molecular weight, because it have valuable source of intellectual property. there are many studies in transdermal drug delivery, blood extraction, skin care fields with a micro-needle. existing micro-needle through using silicon, metal, and polymer materials. to make 3-d shape micro-needle mold, inclined uv lithography is used, but this process is complicated to control process condition and its process output ratio is so low. this review suggests the novel process using dicing progression with an inclined sharp edge to make the sharp shape of microneedle information. and the optical assessment module is made for evaluating the drug delivering ratio according to the needle length and insertion times. this estimation module has a water chamber and membrane to copy the drug delivery mechanism. we can discover that the drug delivering ratio can enlarge when use a longer needle as the surface area with drug sticking can be augmented."
Troensegaard Nielsen, K., Huss Eriksson, A., Funch Carlsen, M., Engell, K., Jansson, J., Petersson, K., … Kemp, P.. (2019). 387 Ex Vivo Visualization and Extended Drug Release from a Dissolvable Microarray. Journal of Investigative Dermatology

Plain numerical DOI: 10.1016/j.jid.2019.07.389
DOI URL
directSciHub download

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"The aim of the study was to investigate a dissolvable microarray (ma) patch in terms of skin insertion and drug release in ex vivo human skin for 6 days and in vivo using minipigs for 4 days. the patches contain polymeric, microscopic arrays composed of a fast dissolving drug-free backing layer and slowly dissolving drug containing tips. the calcipotriol and betamethasone dipropionate (bdp) is encapsulated in the tip and delivered in a pain-free and minimally invasive manner by micro-perforation of the stratum corneum with 500 mum long microneedles. ma needles were visualized by scanning electron microscopy (sem) and skin penetration was studied using reflectance confocal microscopy (rcm). to study the extent and duration of drug release from the mas, a single application of a patch was compared both ex vivo and in vivo to daily application of a gel containing the same active pharmaceutical ingredients. drug release was assessed at several time points after application by quantifying target engagement (te) biomarkers and drug metabolism reflecting free drug available in the viable skin. thus, calcipotriol release was assessed by quantifying the vitamin d (vitd) te biomarkers cyp24a1 and cd14 by qpcr, and bdp release was assessed through quantification of a bdp metabolite. rcm showed efficient penetration of the ma patches into the upper dermis. the observed vitd te biomarkers and bdp metabolite levels were similar for a single applied ma patch compared to daily treatment with the comparator, daivobet gel for up to 6 days in ex vivo human skin and up to 4 days in minipigs. studies on calcipotriol and bdp containing ma patches in human skin explants and gottingen minipigs showed prolonged vitd target engagement and elevated bdp metabolite levels, on par with once daily application of the comparator daivobet gel. the ma patches are likely to offer a convenient treat-and-go approach with reduced dosing frequency and are currently in phase 1 clinical development in psoriasis.copyright © 2019"
Wu, L., Shrestha, P., Iapichino, M., Cai, Y., Kim, B., & Stoeber, B.. (2021). Characterization method for calculating diffusion coefficient of drug from polylactic acid (PLA) microneedles into the skin. Journal of Drug Delivery Science and Technology

Plain numerical DOI: 10.1016/j.jddst.2020.102192
DOI URL
directSciHub download

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“Microneedles are designed for piercing the stratum corneum and delivering drugs into the epidermis and dermis layers of the skin. their micrometric dimension causes minor or negligible stimulations to sensory nerve fibers in the dermis layer of the skin, making drug administration through microneedles less painful compared to conventional hypodermic needle injection. with the advancement of microneedle related research, an increasing number of drugs are using microneedle-mediated drug delivery in the topical area of the skin, including localized delivery of some highly toxic drugs. it is essential to understand drug diffusion from microneedles to skin to avoid unwanted spread of toxic drugs in non-infected areas. this work aims to 1) deliver into the skin tissue fluorescent rhodamine b as a model drug from coated polylactic acid (pla) microneedles and dissolvable microneedles; 2) detect and depict the concentration distribution of the model drug from two types of microneedles into the skin tissue respectively; 3) determine a reliable diffusion coefficient of the model drug based on a constant source diffusion model and a limited source diffusion model for dissolvable microneedles and coated pla microneedles, respectively. dissolvable microneedles and coated pla microneedles were designed and fabricated by a novel methodology combining 3d printing, chemical etching, micro-molding and drop coating. rhodamine b was chosen as the model drug to enable fluorescent detection. two types of microneedles were mounted to a single patch and inserted into porcine skin to deliver the model drug. after microneedle removal, confocal microscopy was used to monitor the fluorescence intensity of rhodamine b in the skin tissue. based on an intensity-concentration calibration and two diffusion models, the diffusion coefficients of rhodamine b from the constant source (dissolvable microneedles) and limited source (coated pla microneedles) to the dermis layer of porcine skin were inferred to be from 3.1×10?8 to 3.6×10?8 cm2/s. this characterization method is expected to offer medical personnel a quantitative understanding of the diffusion process related to microneedle-mediated transdermal drug delivery.”
Griffin, P., Elliott, S., Krauer, K., Davies, C., Rachel Skinner, S., Anderson, C. D., & Forster, A.. (2017). Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects. Vaccine

Plain numerical DOI: 10.1016/j.vaccine.2017.10.021
DOI URL
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“Most vaccinations are performed by intramuscular injection with a needle and syringe. however, this method is not ideal due to limitations, such as the risk of needle-stick injury, the requirement for trained personnel to give injections and the need to reconstitute lyophilized vaccines. therefore, we tested an alternative delivery technology that overcomes the problems with needle and syringe. the nanopatchTM is an array of 10,000 silicon micro-projections per cm2 that can be dry-coated with vaccine for skin delivery. the high number and density of micro-projections means that high velocity application is required to achieve consistent skin penetration. before clinically testing a vaccine

nanopatch, this study tests the safety, tolerability and acceptability/utility of uncoated and excipient-coated nanopatches in healthy adults. nanopatches were applied to skin of the upper arm and volar forearm and left in contact with the skin for two minutes before removal. the application sites were assessed for local skin response over 28 days. acceptability interviews were also performed. no unexpected adverse events directly related to the nanopatch application were reported. all applications of the nanopatch resulted in an expected erythema response which faded between days 3 and 7. in some subjects, some skin discolouration was visible for several days or up to 3 weeks after application. the majority (83%) of subjects reported a preference for the nanopatch compared to the needle and syringe and found the application process to be simple and acceptable. on a pain scale from 0 to 10, 78% of applications were scored ‘0’ (no pain) with the average scores for less than 1. the results from this study demonstrate the feasibility of the nanopatch to improve vaccination by showing that application of the product without vaccine to human skin is safe, tolerable and preferred to needle and syringe administration. clinical trial registry id: actrn1261500083549.”
Kesarwani, A., Yadav, A. K., Singh, S., Gautam, H., Singh, H. N., Sharma, A., & Yadav, C.. (2013). THEORETICAL ASPECTS OF TRANSDERMAL DRUG DELIVERY SYSTEM. Bulletin of Pharmaceutical Research

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“Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver the drug through the skin in order to achieve systemic absorption of drug at a predetermined rate over a prolonged period of time. its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. there are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. due to technological advancement, many new techniques which have attained attention are iontophoresis, phonophoresis, electroporation micro needles etc. different types of transdermal patches can be prepared by varying methods. transdermal patches can be evaluated by interaction studies, folding endurance, thickness of the patch, weight uniformity, drug content and in vitro studies. this review covers general aspects like advantages, methods of preparation of transdermal patches, evaluation, basic components of transdermal drug delivery system.”
Rana, R., Saroha, K., Handa, U., Kumar, A., & Nanda, S.. (2016). Transdermal Patches as a tool for permeation of drug through skin. Journal of Chemical and Pharmaceutical Research

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“For many decades for the treatment of disease many of the dosage form are using which are including tablets, capsules, pills, creams, ointments, liquids, injectables. to maintain the concentration of drug it is necessary to take these types of dosage form several times of day. a novel drug delivery system thus aim at releasing one or more drug continuously at a predetermined pattern for a fixed period of time, either systematically or to a specific target organ. transdermal drug delivery system includes all topically administered drug formulations intended to deliver the active ingredients into the circulation. a patch contained high dose of drug which is retained on the skin for prolonged period of time. drug from patch enters into blood flow via diffusion process. skin contains 10-70 hair follicles and 200-250 sweat ducts per cm 2 of the skin so it is easily accessible by drugs. drug can penetrate through skin via three pathways-through hair follicles, sebaceous gland, and sweat ducts. its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. there are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. due to technological advancement, many new

techniques which have attained attention are iontophoresis, phonophoresis, electroporation and micro needles etc. this review covers general aspects regarding transdermal patches like advantages, basic components of transdermal drug delivery system, methods of preparation of transdermal patches and evaluation."
Museau, M., Butdee, S., Vignat, F., & others. (2011). Design and Manufacturing of Microneedles. Toward Sustainable Products?. Asian International Journal of Science and Technology in Production and Manufacturing Engineering

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"Microneedles can be used for drugs delivery instead of conventional hypodermic needles with some advantages: they cause less pain and skin irritation, the risk of transmitting infection is less important and they can be more economical to manufacture. a presentation of different families of microneedles and their advantages compared to conventional needles can be found in the first part of this paper. then, current manufacturing processes of microneedles are presented and discussed, followed by the proposition of an innovative manufacturing strategy to make a patch composed of hollow microneedles. this strategy combines micro machining processes to make an insert that will be use during injection moulding. at last, the concept of sustainability is presented with the aim to start discussion on the sustainable aspects of the designed microneedles, and then provide some answers"
Sun, F., Koh, K., Ryu, S. C., Han, D. W., & Lee, J.. (2012). Biocompatibility of nanoscale hydroxyapatite-embedded chitosan films. Bulletin of the Korean Chemical Society

Plain numerical DOI: 10.5012/bkcs.2012.33.12.3950
DOI URL
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"In order to improve the bioactivity and mechanical properties of hydroxyapatite (hap), chitosan (chi) was in situ combined into hap to fabricate a composite scaffold by a sublimation-assisted compression method. a highly porous film with sufficient mechanical strength was prepared and the bioactivity was investigated by examining the apatite formed on the scaffolds incubated in simulated body fluid. in addition, the cytotoxicity of the hap/chi composite was studied by evaluating the viability of murine fibroblasts (l-929 cells) exposed to diluted extracts of the composite films. the apatite layer was assessed using scanning electronic microscopy, inductively coupled plasma-optical emission spectrometry and weight measurement. composite analysis showed that a layer of micro-sized, needle-like crystals was formed on the surface of the composite film. additionally, the wst-8 assay after l-929 cells were exposed to diluted extracts of the composite indicated that the hap/chi scaffold has good in vitro cytocompatibility. the results indicated that hap/chi composites with porous structure are promising scaffolding materials for bone-patch engineering because their porous morphology can provide an environment conductive to attachment and growth of osteoblasts and osteogenic cells."
Micro-Needle Drug Patch Uses Inkjet Technology. (2007). Biomedical Instrumentation & Technology

Plain numerical DOI: 10.2345/0899-8205(2007)41[431:mdpuit]2.0.co;2
DOI URL
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Sharquie, K. E., Noaimi, A. A., & Al-Khafaji, Z. N.. (2016). Direct Transplant of Melanocytes from Normal Donor Area into Vitiligenous Recipient Area by Intralesional Injection of Melanocytes Using Spade Like Needle Technique. Journal of Cosmetics, Dermatological Sciences and Applications

Plain numerical DOI: 10.4236/jcdsa.2016.64022
DOI URL
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“Background: vitiligo is a common autoimmune inflammatory skin disease, where there are different surgical techniques for treatment of stable patches of vitiligo .objective: to find non-costly, minimally invasive, simple technique by direct melanocytes transplant by spade needle technique in treatment of vitiligo. patients and methods: this interventional, therapeutic, comparative study was done in department of dermatology, baghdad teaching hospital, baghdad, iraq from april 2014-march 2015. twenty patients with localized, generalized and segmental vitiligo were included. full history and examination for each patient was done with 4 (20%) males and 16 (80%) females and their ages ranged from 9 – 40 (23.15 ? 11.44) years. forty one patches in 20 patients treated by spade grafting technique and the donor and recipient sites were demarcated and anesthesia done by xylocaine 2% with adrenalin 1:100,000. transplantation was started by using disposable needle gauge 18 (the sharp end of needle was cut by a scissor to make it a spade like) with medical syringe 5 ml supplied with normal saline. the micro-pieces were taken from donor site and transplanted directly, easily and rapidly into dermis of recipient site and followed by pushing normal saline and the procedure was repeated to cover all recipient sites with 5 mm distance between injection points. the surface area of the lesions was calculated and the reduction rate was estimated every month till the end of the 4th month period of the treatment. results: including 41 patches in 20 patients with the surface area of the patches ranged from 1.5 – 90 cm2 (13.78 ? 17.57) cm2. the mean ?sd of surface area of lesions was decreased from 13.78 ? 17.57 cm2 at baseline visit to 13.61 ? 17.48 cm2 at the second visit (after 2 weeks) which was statistically significant (p value ??0.001). the mean surface area continued to be reduced till reaching 12.20 ? 15.68 cm2 at the third visit and 12.01 ? 15.55 cm2 at the fourth visit. all were statistically significant when compared to baseline visit. there was reduction in s”
Sun, Y., Chen, M., Yang, D., Qin, W., Quan, G., Wu, C., & Pan, X.. (2021). Self-assembly nanomicelle-microneedle patches with enhanced tumor penetration for superior chemo-photothermal therapy. Nano Research

Plain numerical DOI: 10.1007/s12274-021-3817-x
DOI URL
directSciHub download

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“Nanomedicine with high specificity has been a promising tool for cancer diagnosis and therapy. however, the successful application of nanoparticle-based superficial cancer therapy is severely hindered by restricted deep tumor tissue accumulation and penetration. herein, a self-assembly nanomicelle dissolving microneedle (dmn) patch according to the ‘nano in micro’ strategy was conducted to co-deliver a first-line chemotherapeutic agent paclitaxel (ptx), and a photosensitizer ir780 (ptx/ir780-nms @dmns) for chemo-photothermal synergetic melanoma therapy. upon direct insertion

into the tumor site, dmns created a regular and multipoint three-dimensional drug depot to maximize the tumor accumulation. accompanied by the dmn dissolution, the composition of the needle matrixes self-assembled into nanomicelles, which could efficiently penetrate deep tumor tissue. upon laser irradiation, the nanomicelles could not only ablate tumor cells directly by photothermal conversion but also trigger ptx release to induce tumor cell apoptosis. in vivo results showed that compared with intravenous injection, ir780 delivered by ptx/ir780-nms @dmns was almost completely accumulated at the tumor site. the antitumor results revealed that the ptx/ir780-nms @dmns could effectively eliminate tumors with an 88% curable rate without any damage to normal tissues. this work provides a versatile and generalizable framework for designing self-assembly dmn-mediated combination therapy to fight against superficial cancer. [figure not available: see fulltext.]”
Economidou, S. N., Pere, C. P. P., Reid, A., Uddin, M. J., Windmill, J. F. C., Lamprou, D. A., & Douroumis, D.. (2019). 3D printed microneedle patches using stereolithography (SLA)for intradermal insulin delivery. Materials Science and Engineering C

Plain numerical DOI: 10.1016/j.msec.2019.04.063
DOI URL
directSciHub download

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“3D printed microneedle arrays were fabricated using a biocompatible resin through stereolithography (sla)for transdermal insulin delivery. microneedles were built by polymerising consecutive layers of a photopolymeric resin. thin layers of insulin and sugar alcohol or disaccharide carriers were formed on the needle surface by inkjet printing. the optimization of the printing process resulted in superior skin penetration capacity of the 3d printed microneedles compared to metal arrays with minimum applied forces varying within the range of 2 to 5 n. micro-ct analysis showed strong adhesion of the coated films on the microneedle surface even after penetration to the skin. in vivo animal trials revealed fast insulin action with excellent hypoglycaemia control and lower glucose levels achieved within 60 min, combined with steady state plasma glucose over 4 h compared to subcutaneous injections.”
Bora, P., Kumar, L., & Bansal, A. K.. (2008). Microneedle Technology for Advanced Drug Delivery : Evolving vistas. CRIPS

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“Transdermal patches are considered as a viable alternative to deliver the drugs having poor oral bioavailability. however, the success of transdermal patches is limited only to lipophilic and/or low molecular weight drugs. a number of advanced drug delivery systems including iontophoresis, sonophoresis, electroporation and microneedle technology have been developed for the penetration of even large molecular weight and/or hydrophilic compounds across the skin. micron scale needles assembled on a transdermal patch are proposed as a hybrid between hypodermic needles and transdermal patches to overcome the individual limitations of both the injections as well as patches. a variety of methods including poke with patch, coat and poke are possible for the fabrication of microneedle system. the technique has a promising future and is considered as a dosage form of interest for vaccines, peptides and genes.”
Ravi, S., Sharma, P. K., & Bansal, M.. (2011). A review: Transdermal drug delivery of nicotine. International Journal of Drug Development and Research

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“Cigarette smoking has been the leading cause of premature death and illness in many industrialized country in the world, while the u.s. alone registers more than 4,00,000 deaths each year. the nicotine patch serves to deliver a constant dose of nicotine across the skin that helps to relieve the symptoms which are associated with tobacco withdrawal. further, the use of carbon nanotube membranes and micro needle based transdermal drug delivery has lead to the great advancements. some of the main advantages of transdermal drug delivery are bypassing of hepatic first pass metabolism, maintenance of steady plasma level of the drug and enhancement of therapeutic efficiency. © 2010 ijddr.”
Shende, P., Sardesai, M., & Gaud, R. S.. (2018). Micro to nanoneedles: a trend of modernized transepidermal drug delivery system. Artificial Cells, Nanomedicine and Biotechnology

Plain numerical DOI: 10.1080/21691401.2017.1304409
DOI URL
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“The transdermal route of drug delivery is convenient, pain-free and follows controlled rate release pattern. however, many therapeutically active drugs cannot cross the stratum corneum effectively. lipophilic drugs like nifedipine cross the outer skin barrier easily and polar drugs, such as epinephrine are ineffective in showing the same effect. due to these reasons, advancements in drug delivery have taken place to deliver a wide range of drugs, especially macromolecules through the transdermal route and directly into systemic circulation bypassing hepatic metabolism and git degradation. so there is a need for advanced drug delivery systems like microneedles and nanoneedles through transdermal route. these tiny needles will also serve as non-toxic, safe and stable systems for advanced drug delivery. thus, macro to nanoformulation is the fast emerging fields nowadays. these have additional advantages to transdermal patches, such as better penetration, permeation, controlled release and direct delivery to the cytoplasm.”
Chen, X., Kositratna, G., Zhou, C., Manstein, D., & Wu, M. X.. (2014). Micro-fractional epidermal powder delivery for improved skin vaccination. Journal of Controlled Release

Plain numerical DOI: 10.1016/j.jconrel.2014.08.006
DOI URL
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“Skin vaccination has gained increasing attention in the last two decades due to its improved potency compared to intramuscular vaccination. yet, the technical difficulty and frequent local reactions hamper its broad application in the clinic. in the current study, micro-fractional epidermal powder delivery (epd) is developed to facilitate skin vaccination and minimize local adverse effects. epd is based on ablative fractional laser or microneedle treatment of the skin to generate microchannel (mc) arrays in the epidermis followed by topical application of powder drug/vaccine-coated array patches to deliver drug/vaccine into the skin. the novel epd delivered more than 80% sulforhodamine b (srb) and model antigen ovalbumin (ova) into murine, swine, and human skin within 1 h. epd of ova induced anti-ova

antibody titer at a level comparable to intradermal (id) injection and was much more efficient than tape stripping in both delivery efficiency and immune responses. strikingly, the micro-fractional delivery significantly reduced local side effects of lps/cpg adjuvant and bcg vaccine, leading to complete skin recovery. in contrast, id injection induced severe local reactions that persisted for weeks. while reducing local reactogenicity, epd of ova/lps/cpg and bcg vaccine generated a comparable humoral immune response to id injection. epd of vaccinia virus encoding ova induced significantly higher and long-lasting interferon ?-secreting cd8 + t cells than id injection. in conclusion, epd represents a promising technology for needle-free, painless skin vaccination with reduced local reactogenicity and at least sustained immunogenicity. © 2014 elsevier b.v."
Raghuraman, V., & Pandey, V. P.. (2014). Approaches and Significance of Transdermal Drug Delivery Systems: a Review. International Journal of Pharmaceutical Sciences and Research

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"Transdermal drug delivery system (tdds) is the most innovative and novel drug delivery systems by penetrating through the skin by increasing the scope of molecules that can be delivered. tdds that traditionally uses a patch containing loaded drug substances pressed on to the skin is convenient, painless and non-invasive, to avoid gastro intestinal (gi) tract toxicity (peptic ulcer disease). transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation which often causes undesirable side effect. the number of medications and the ways in which they can be administered have expanded dramatically over the years. one such advancement is the development of transdermal patch delivery systems. transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. various products of tdds are in use by applying approaches like micro needles, abrasion, micro scission, jet delivery, iontopher's, electroportation, ultrasound and radiofrequency. the present drug delivery is highly significant if compared to oral route for less side effect, better bioavailability and longer duration of action."
Sriperumbudur, K. K., Koester, P. J., Stubbe, M., Tautorat, C., Held, J., & Gimsa, J.. (2009). Local Electroporation of Single Adherent Cells by Micro-Structured Needle Electrodes. In proceedings of the comsol

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"In spite of its low throughput, patch-clamp is the established method for intracellular measurements of the transmembrane potential. to address this problem, we have developed new biosensor-chips with micro-structured needle electrodes (mnes). mne-penetration of single cells growing on the mne-tips leads to a situation comparable to the whole-cell mode in classical patch clamp. mne-penetration was accomplished by local micro-invasive needle electroporation (lomine; koester et al., 2008; baumann et al., 1998a and b). in this paper, we simulate the field and potential distributions around the mne before lomine assuming reasonable cell and medium parameters for a cell being in contact with the needle via focal adhesion points."
Szymura, T. H., Dunajski, A., Aman, I., Makowski, M., & Szymura, M.. (2007). The spatial pattern and microsites requirements of Abies alba natural regeneration in the Karkonosze Mountains. Dendrobiology

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“Progeny of four adult silver firs, which were an admixture in norway spruce (picea abies) stand was, analyzed. the study was done in lower mountain zone of the karkonosze (giant mts.) national park (sw poland). the seedlings occurred in two clumps related to the position of adult trees, whereas spatial pattern of the seedlings inside each clump was random. the seedlings were spaced mainly in distances 5-25 from the nearest adult tree. the maximal distance was up to 50 m. most seedlings were established in accordance with main wind directions. also, in these directions seedlings were more distant from adult trees than in other directions. the seedlings grew in better light environment (12% of ppfd) than average (9,6% ppfd). this effect was statistically significant. the height increment of the seedlings was low and was not correlated with light conditions. similarly, there was not any correlation between the apical dominance ratio and light. the lack of this correspondence we attributed to browsing. the silver fir seedlings were significantly underrepresented in patches of vaccinium myrtillus, on raw needles, under crown of adult trees and in concave micro-relief form. the underrepresentation in the places covered by canopy and in patches of bilberry we related to the indirect effect of continuous browsing, which leads to higher seedlings mortality in more shaded places and sites of stronger competition between forest floor vegetation and silver fir seedlings.”
Nazari, K., Mehta, P., Arshad, M. S., Ahmed, S., Andriotis, E. G., Singh, N., … Ahmad, Z.. (2020). Quality by design micro-engineering optimisation of NSAID-loaded electrospun fibrous patches. Pharmaceutics

Plain numerical DOI: 10.3390/pharmaceutics12010002
DOI URL
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“The purpose of this study was to apply the quality by design (qbd) approach to the electrospinning of fibres loaded with the nonsteroidal anti-inflammatory drugs (nsaids) indomethacin (indo) and diclofenac sodium (diclo). a quality target product profile (qtpp) was made, and risk assessments (preliminary hazard analysis) were conducted to identify the impact of material attributes and process parameters on the critical quality attributes (cqas) of the fibres. a full factorial design of experiments (doe) of 20 runs was built, which was used to carry out experiments. the following factors were assessed: drugs, voltage, flow rate, and the distance between the processing needle and collector. release studies exhibited indo fibres had greater total release of active drug compared to diclo fibres. voltage and distance were found to be the most significant factors of the experiment. multivariate statistical analytical software helped to build six feasible design spaces and two flexible, universal design spaces for both drugs, at distances of 5 cm and 12.5 cm, along with a flexible control strategy. the current findings and their analysis confirm that qbd is a viable and invaluable tool to enhance product and process understanding of electrospinning for the assurance of high-quality fibres.”
Kündig, T. M., Bot, A., & Senti, G.. (2012). Intralymphatic vaccination. In Gene Vaccines

Plain numerical DOI: 10.1007/978-3-7091-0439-2_10
DOI URL
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“The immune response is initiated by dendritic cells and other antigen-presenting cells. these cells are present in nearly all organs and tissues of the body, so that theoretically any organ or tissue could serve as a route for vaccine administration. the choice of route is therefore mainly based on practical aspects. using conventional needle and syringe the subcutaneous or intramuscular route are standard. the dermis and especially the epidermis are technically more difficult to target, but are likely to gain more interest due to the recent development of micro-needle patches and needle free injection devices. vaccine administration via mucosal surfaces such as nasal or oral vaccination represents another option for needle free vaccine administration. while all the above mentioned routes of administration have been proven to work and protect against childhood diseases, influenza and many other infectious agents, the discussion and comparison of these different routes usually focuses on patient convenience, reduction of pain and distress for children, cost and on the possibility for mass vaccination. in this review, however, we would like to focus on how the route of administration can enhance the efficacy of vaccination, in clinical indications that are benefiting to a much lesser extent from conventional vaccination. especially in therapeutic vaccination, i.e., in a smaller patient number that already suffers from a disease, vaccination efficiency rather than convenience is the main issue. this is particularly the case in therapeutic cancer vaccines and in allergen specific immunotherapy. intralymphatic vaccination is a strategy to maximize immunogenicity and therefore vaccine efficacy. the main part of this review will discuss this long known vaccination route and its clinical applicability in therapeutic vaccination, with a special focus on gene vaccines.”
Kang, G., Kim, S., Yang, H., Jang, M., Chiang, L., Baek, J. H., … Jung, H.. (2019). Combinatorial application of dissolving microneedle patch and cream for improvement of skin wrinkles, dermal density, elasticity, and hydration. Journal of Cosmetic Dermatology

Plain numerical DOI: 10.1111/jocd.12807
DOI URL
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“Background: dissolving microneedles (dmns), microscale needles with a biodegradable polymer matrix, have been widely investigated for transdermal drug delivery. however, the restricted drug loading space of dmns limited the delivery of the desired quantity of active compounds. in this study, we developed novel combinatorial therapies involving sequential application of adenosine-loaded dmn (ad-dmn) patches and a topical adenosine-loaded cream (ad-cream). the application of dmns created skin channels, which delivered encapsulated drugs from both the dmns and cream. the use of combinatorial therapies can maximize drug delivery. methods: to compare the efficacy of combinatorial therapies and ad-cream application, a double-blind clinical test was conducted over 10 weeks on 21 females with wrinkles around their eyes, and the skin parameters such as wrinkles, dermal density, elasticity, and hydration were analyzed. the skin irritation test was assessed by expert interviewers to elucidate undesirable side effects. results: the combinatorial therapies showed statistically significant efficacy for the improvement of average depth of wrinkles, dermal density, elasticity, and hydration after an 8-week application ($p < 0.001$). adverse effects on the skin were not observed in any subject during the test period. conclusion: the efficacy and safety results showed that the combinatorial

therapies were a safe and outstanding innovation for the optimization of transdermal therapy."
Chitra, K. P., Bhimavarapu, R., Rani.B, S., Priyadarshini, I., & Reddy, A. B.. (2011). MICRONEEDLES: AN EFFECTIVE TECHNIQUE FOR TRANSDERMAL DRUG DELIVERY. International Journal of Biomedical Research

Plain numerical DOI: 10.7439/ijbr.v2i8.127
DOI URL
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"Optimization of drug delivery through human skin is important in modern therapy. with limitations of oral drug delivery, pain and needle phobias associated with traditional injections drug delivery research has focused on transdermal delivery route. a new approach to transdermal delivery that acts as a bridge between the user friendless of patches and the broad effectiveness of hypodermic needles has recently received attention.by using needles of micron dimensions, termed microneedles, skin can be pierced to effectively deliver the drugs, the mechanism of action is based on temporary mechanical disruption of skin. the drug, in the form of biomolecules, is encapsulated within the micro needles, which are then inserted into the skin in the same way a drug like nitroglycerine is released into the bloodstream from a patch. the needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. the present review focus on various studies related to micro needles for transdermal drug delivery and technology applications in various fields."
Severe systemic reaction associated with skin microneedling therapy in 2 sisters: A previously unrecognized potential for complications?. (2013). Journal of the American Academy of Dermatology

Plain numerical DOI: 10.1016/j.jaad.2012.12.904
DOI URL
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"Skin microneedling creates microconduits through the epidermis, resulting in neocollagenesis and neovascularization in the papillary dermis, used to treat acne scars, stretch marks and for facial rejuvenation. two sisters, aged 34 and 44 years, underwent facial skin microneedling by a trained practitioner in a criss-cross manner, following skin cleansing and topical anesthetic cream application. a separate sealed single-use, presterilized, ce marked, fda registered drum-shaped roller (192 stainless steel microneedles; 8 rows, 1.5 mm long, 0.25 mm wide) was used on each woman. both developed marked neck lymphadenopathy within 24 hours of the procedure. in addition, the older sister experienced immediate intense localized erythema and prolonged pinpoint bleeding, malaise, and headache. systemic antibiotic treatment was unhelpful. she deteriorated further in the following 2 weeks, developing a florid erythematous papular rash on the face, with progression to the trunk and limbs and associated facial edema. hospitalization with oral and topical corticosteroid treatment led to gradual improvement over 2 weeks. infective and autoimmune screens were negative. incisional biopsy revealed a non-specific, chronic inflammatory infiltrate. patch testing to british standard series, topical anesthetic cream, aftercare products and sunblock used, showed reaction to nickel sulphate (d4++), already known to the patient. on manufacturer inquiry, the roller microneedles were found to contain up to 0.006% sulphur and 8% nickel bound to surgical grade stainless steel alloy. skin

microneedling is considered a safe alternative to more invasive cosmetic procedures, with no down time and minimal side effects of mild transient erythema and bruising. rarer adverse effects have been attributed to: nonsterilized devices or roller reuse (microbial infections); nickel-plated microneedles (allergic contact dermatitis); inexpensive metal micro-needles (needle breakage); enhanced needle penetration caused by microneedle length >2 mm or excessive operator force (trauma). low sulphur stainless steel alloys containing nickel are thought to pose little or no risk in short term contact with nickel-sensitive individuals. to our knowledge, this is the first report of serious systemic reaction to treatment with a ce marked, fda registered microneedle roller in 2 sisters, highlighting the need for caution in offering microneedling as a risk-free option in cosmetic practice."
M., B., E., D., M., C., E., F., A., G., & F., G.. (2009). An innovative transdermal drug delivery device for the treatment of chronic diseases. Experimental Dermatology

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"In chronic disease, such as in type 1 diabetes (t1d), the final goal indicated by physicians is to maintain an adequate blood level of glucose by utilizing a continuous and modulated administration of insulin, over time. it is essential to find an effective and personalised drug administration since the usual pharmaceutical formulations are unable, at the same time, to achieve these goals. an appealing alternative to hypodermic injections could be transdermal drug delivery (tdd) using patches, although the limitation for insulin is represented by its high molecular weight. tdd seems to be an attractive option but the bioavailability of insulin will have to be optimized compared with that achieved by subcutaneous injection. we designed an innovative biomedical micro-structured device for controlled, painless, tdd, based on a matrix of hollow micro-needles in order to insert the drug just below the epidermal layers and let it diffuse into of papillary dermis blood vessels. in the complete device drug flux rate will be controlled by the help of a tuneable, micro-structured pump. an existing non-miniaturised prototype has been produced and some preliminary skin piercing and infusion tests have already been performed on human skin biopsies. in particular we delivered a green fluorochrome-labelled insulin, monitoring the drug diffusion in the skin. samples were immediately frozen in liquid nitrogen and cryostate sections were obtained. skin sections demonstrated piercing of the epidermis and infusion of insulin within epidermis and dermis reaching the dermal capillaries."
Faraji Rad, Z., Prewett, P. D., & Davies, G. J.. (2021). Rapid prototyping and customizable microneedle design: Ultra-sharp microneedle fabrication using two-photon polymerization and low-cost micromolding techniques. Manufacturing Letters

Plain numerical DOI: 10.1016/j.mfglet.2021.10.007
DOI URL
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"In recent years, interest in microneedle devices for drug and vaccine delivery and point-of-care diagnostics has grown due to low cost, convenience and minimal invasiveness. a cluster of miniature needles on a small patch could enhance the quality of human health care, revolutionizing test and drug and vaccine delivery systems. however, current fabrication methods are not viable for cost-effective large-scale manufacture. this study reports fabrication of ultra-sharp microneedles with microfluidic channels using two-photon polymerization (2pp) which enables flexible designs with resolution down to 100 nm. the technique is ideally suited to prototyping and the fabrication of master molds from which

elastomeric negative-molds have been used in a rapid micromolding technique to make batches of ultra-sharp microneedles. this micromolding process has mass manufacturing potential."
Olatunji, O., & Das, D. B.. (2019). Drug delivery using microneedles. In Comprehensive Biotechnology

Plain numerical DOI: 10.1016/B978-0-444-64046-8.00311-6
DOI URL
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"This article aims to review various aspects of the technique of using microneedles for drug delivery. drug delivery using microneedles is a relatively new form of transdermal drug delivery that not only permits painless drug delivery but also increases the range of drugs that can be delivered through the skin. they are also likely to improve neural, ocular, and intravascular drug delivery in addition to their other benefits outside drug delivery. microneedles were first applied to transdermal drug delivery in the late 1990s, making this a novel idea at that time. different techniques can be applied for drug delivery while using microneedles. these are the poke with patch, coat and poke, and dip and scrape approaches, encapsulating the drugs within the dissolving microneedles and flowing through the lumen of hollow microneedles. a range of materials have been used to fabricate microneedles such as silicon, metal, glass, and polymer using the microelectromechanical systems (mems) fabrication methods. a micro-dip coating method has been introduced for coating of solid microneedles, and this has been shown to be an efficient method as the drugs adhere well to the needle surface and do not rub off on insertion into the skin, rather they dissolve within the epidermis as desired. vaccines, proteins, dna, vitamins, and calcein have been successfully coated on solid microneedles, and experiments on rats have shown that drugs delivered using coated microneedles do reach the bloodstream and have the expected pharmacologic effects."
Waghulde, S., Naik, P. P., Gorde, N., Juvatkar, P., Shirodkar, P. Y., & Kale, M. K.. (2013). Development, recent inventions and evaluation techniques of transdermal drug delivery system – A review. International Journal of Pharmaceutical and Phytopharmacological Research

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"Patch-based transdermal drug delivery offers a convenient way to administer drugs without the drawbacks of standard hypodermic injections relating to issues such as patient acceptability and injection safety. however, conventional transdermal drug delivery is limited to therapeutics where the drug can diffuse across the skin barrier. by using miniaturized needles, a pathway into the human body can be established which allow transport of macromolecular drugs such as insulin or vaccines. the human skin is a readily accessible surface for drug delivery. skin of an average adult body covers a surface of approximately 2 m 2 and receives about one-third of the blood circulating through the body. over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. the human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. it is one of the most readily accessible organs of the human body. the potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. during the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. modifications have been mostly

limited to refinements of the materials used. the present article development, recent inventions and evaluation techniques of transdermal drug delivery system."
S., X., H., Z., H., Z., A.S., P., X., Z., J., Z., & J.A., R.. (2018). A wearable, flexible, conformable and depth-modulated phototherapy device: Initial application in morphea. Journal of Investigative Dermatology

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"Morphea is a localized, sclerosing skin condition that can extend deep into muscle and fascia. while uva-1 (340-400 nm) phototherapy is often effective, these units are not widely available, expose unaffected skin to uva-1, and require several weeks until treatment response. thus, there is a need for new uva-1 systems that offer faster response times, greater efficacy, targeted therapy and increased convenience. in morphea, uva-1 leads to the upregulation of collagenase and ifn?, leading to decreased collagen i, collagen iii, and tgf? expression. however, the intensity of uva-1 attenuates to 1% at 190 ?m in human skin, which is more superficial than the depth of disease in many morphea cases. thus, we hypothesize that deeper uva-1 delivery will improve efficacy and response time. using advanced techniques in flexible electronics, we have developed a soft, conformable, and depth-modulated uva-1 phototherapy device. the devices top layer has an array of uva-1 light emitting diodes (spectral peak output: 360-nm) fully embedded within a flexible silicone substrate. the power intensity output is 35 mw/cm2 with uniform distribution across the entire patch as confirmed by a uva light meter. the bottom layer includes a dense array of microneedles from poly-lactic-co-glycolic-acid (plga), a polymer enabling 99% of uva transmittance, which create micro-channels 700 ?m for deeper uva-1 delivery into the skin. optical modeling, confirmed by confocal microscopy in agarose, demonstrates that the plga microneedle waveguides increase light transmission by 250% along the z-axis along the length of the needles. the system can conform to any curvilinear body surface and be cut to any shape or size. future clinical testing will validate the safety and efficacy of the system compared to standard uva-1 phototherapy."
Nishimura, M., Akai, T., Hotta, A., Ishida, M., & Kamon, M.. (2018). Development of gas-permeable/waterproof sheet and its application as a cover sheet of putrefactive-radioactive contaminated waste. In 11th International Conference on Geosynthetics 2018, ICG 2018

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"We have newly developed a gas-permeable/waterproof sheet (gpws), comprising a micro-porous sheet which is waterproof and with gas permeability, coated with nonwovens to protect and reinforce this center sheet, and have conducted many kinds of experiments in both laboratories and fields. gpws has been widely applied as a cover sheet for temporary storage sites of putrefactive-radioactive contaminated waste due to the accident of fukushima dai-ichi nuclear power station. although gpws itself has waterproofness based on micro-porous sheet, it is quite difficult to achieve sufficient waterproofness in seams of gpwss because gpws has needle-punched nonwoven layers that intrinsically have (in-plane) hydraulic transmissivity. in this paper, we first show representative characteristics of gpws, such as waterproofness, gas permeability, and tensile strength. special seaming method of gpwss we developed is also presented. in addition, we developed patch repairing method that is useful for repairing damaged point of gpws by external factor such as birds' pecking and abrasion by excessive stepping. these seaming and patch repairing methods are actually applied to real temporary storage sites of putrefactive- radioactive contaminated waste in which gpws is used as a cover sheet at fukushima site."
G., C., B., H., D., J., M., L., H., Z., Z., D., … Xia, J.. (2015). Pharmacokinetic and pharmacodynamic study of triptolide-loaded liposome hydrogel patch under microneedles on rats with collagen-induced arthritis

. Acta Pharmaceutica Sinica B

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“Triptolide (tp), a major active component of tripterygium wilfordii hook.f. (twhf), is used to treat rheumatoid arthritis (ra). however, it has a narrow therapeutic window due to its serious toxicities. to increase the therapeutic index, a new triptolide-loaded transdermal delivery system, named triptolide-loaded liposome hydrogel patch (tp-lhp), has been developed. in this paper, we used a micro-needle array to deliver tp-lhp to promote transdermal absorption and evaluated this treatment on the pharmacokinetics and pharmacodynamics of tp-lhp in a rat model of collagen-induced arthritis (cia). the pharmacokinetic results showed that transdermal delivery of microneedle tp-lhp yielded plasma drug levels which fit a one-compartment open model. the relationship equation between plasma concentration and time was c=303.59×(e-0.064t-e-0.287t). the results of pharmacodynamic study demonstrated that tp-lhp treatment mitigated the degree of joint swelling and suppressed the expressions of fetal liver kinase-1, fetal liver tyrosine kinase-4 and hypoxia-inducible factor-1? in synovium. other indicators were also reduced by tp-lhp, including hyperfunction of immune, interleukin-1? and interleukin-6 levels in serum. the therapeutic mechanism of tp-lhp might be regulation of the balance between th1 and th2, as well as inhibition of the expression and biological effects of vascular endothelial growth factor.”
Volchatova, E. V., Bezrukova, E. V., Kulagina, N. V., Kerber, E. V., Reshetova, S. A., Shchetnikov, A. A., & Filinov, I. A.. (2021). Vegetation history in the lake ilchir basin (East sayan mountains) for the last 8500 years. Geosfernye Issledovaniya

Plain numerical DOI: 10.17223/25421379/18/4
DOI URL
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“Holocene climate is more complex both temporally and spatially than is commonly recognized. pollen records from inland regions are important for understanding past changes in landscapes, assessing the sensitivity of ecosystems to future climatic variations that affect the composition of vegetation and its change over time. high-mountain boreal ecosystems are very vulnerable to climate change, and even minor fluctuations in it can lead to serious natural changes. we carried out analysis of pollen, spores, micro-charcoal particles, conifer stomata, and lithology of an ams 14c-dated core from high-mountain lake ilchir situated in the eastern sayan mountains, in order to reveal changes in vegetation and climate since 8490 cal yr bp. the sediments of 133 cm long core consists of gray silty clay and shows no signs of sedimentary hiatuses. fife bulk sediment samples were dated with an accelerator mass spectrometry (ams) system. the modern vegetation of the lake ilchir basin is ranges from moist forb-grass meadow around the lake to small patches of open larch stands and shrubby birch on the basin slopes. the pollen record presented here is the first continuous and well-dated records from lake ilchir covering the last 8490 cal years, allowing detailed reconstruction of vegetation and environmental dynamics in the region. the results of the pollen analysis and pollen-based vegetation and climate reconstruction suggest that grass-dominated meadow communities prevailed in the lake basin from 8490 to 6000 kyr bp. the absence of larch and fir stomata in the sediments suggests the growth of trees rather far from the lake shore. probably, the climate in the basin was moderately cold with insufficient moisture. the high scots pine pollen percentage in comparison with surface pollen spectra

suggests a higher than today position of the upper boundary of the pine in response of higher-than-present summer insolation. between 6000–3700 kyr bp the climate was characterized by warmer than modern winter seasons and high snow cover, which did not allow the soils to freeze and supported the development of fir in the ilchir lake basin. however, the increased abundance of larch pollen and stomatal cells of its needles in sediments suggest an increased role of larch in the composition of local vegetation and/or its approach to the lake shoreline. expansion of the areas of larch means that climate gradually became sharply continental, more arid. the last 3700 years was characterized …"
Chen, G., Xu, K., Dou, J. J., Yan, J. H., Ju, D. H., Zhao, H. Y., … Hao, B. H.. (2012). Effects of different triptolide formulations given by MEMS micro-needles on skin injury of rheumatoid arthritis rats. Chinese Pharmaceutical Journal

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"OBJECTIVE: to study the effects of different triptolide formulations given by micro electro mechanical systems (mems) micro-needles on skin injury of rheumatoid arthritis rats . methods: three formulations of triptolide were prepared including the aqueous solution of 20% propylene glycol, liposomes, and liposomes hydrogel patch. rats with rheumatoid arthritis induced by collagen ii were used, and 100 and 200 ?m mems micro-needles treatment was performed on left and right sides of rat skin. the lactate dehydrogenase (ldh) activities were measured by ultraviolet spectro-photometric method. results: after processed by mems micro-needle, the ldh activities of ra rat skin did not change obviously ($p > 0.05$). all triptolide formulations increased ldh activities ($p < 0.05$), and the increasement of solution group was largest ($p < 0.001$), followed by lipsomes group ($p < 0.01$) and liposomes hydrogel patch ($p < 0.05$). nevertheless, there was no significant difference between left and right sides of rat skin ($p > 0.05$). conclusion: both 100 and 200 ?m mems micro-needles were safe for enhancement of transdermal delivery in rheumatoid arthritis rats. the skin injury was observably relieved when triptolide was prepared as liposomes hydrogel patch which is a perfect formulation for transdermal delivery of triptolide. copyright 2012 by the chinese pharmaceutical association."
S., W., P.P., N., N., G., P., J., P.Y., S., & M.K., K.. (2013). Development, recent inventions and evaluation techniques of transdermal drug delivery system – A review. International Journal of Pharmaceutical and Phytopharmacological Research

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"Patch-based transdermal drug delivery offers a convenient way to administer drugs without the drawbacks of standard hypodermic injections relating to issues such as patient acceptability and injection safety. however, conventional transdermal drug delivery is limited to therapeutics where the drug can diffuse across the skin barrier. by using miniaturized needles, a pathway into the human body can be established which allow transport of macromolecular drugs such as insulin or vaccines. the human skin is a readily accessible surface for drug delivery. skin of an average adult body covers a surface of approximately 2 m 2 and receives about one-third of the blood circulating through the body. over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. the human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. it is one of the most readily accessible organs of the human body. the potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. during the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. modifications have been mostly

limited to refinements of the materials used. the present article development, recent inventions and evaluation techniques of transdermal drug delivery system."
Ma, B., Gan, Z., & Liu, S.. (2005). Flexible silicon microneedles array for micro fluid transfer. In 2005 6th International Conference on Electronics Packaging Technology

Plain numerical DOI: 10.1109/ICEPT.2005.1564615
DOI URL
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"This paper will report on a new method of using silicon micro needle in bio-medical application. the hollow micro needle array have been designed and fabricated from single crystal silicon for transdermal delivery. the machined micro needles are shank height of 150?m with 250?m center-tocenter spacing. the needle size, density and shape are controlled by independent processing steps. packaging technology incorporates a micro needles array affixed to a polymeric adhesive base. the maximal adhesive patch size is 2 cm2. flow rate test is proved that the polymeric base construction is important to function of micro needles array. glucose solution tests show that surface tension is the dominant force to affect the characters of flow in micro needles channel. © 2005 ieee."
Newswire, P. R.. (2015). Microneedles for Transdermal and Intradermal Drug Delivery, 2014-2030. Lon-Reportbuyer

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; "; LONDON, july 30, 2015 /prnewswire/ — introductiontransdermal delivery via microneedles is increasingly gaining traction as one of the more promising drug delivery technologies. microneedles are of a few hundred microns in size, capable of creating transient pores across the skin by penetrating the stratum corneum layer to deliver molecules. these needles are not big enough to reach the nerve-rich regions of the skin; as a result, the drug delivery is perceived as completely painless and devoid of bleeding. drugs, vaccines, proteins, peptides and other biomolecules are suitable for delivery using the microneedle technology.the market is still in its infancy. so far, only one microneedle based delivery device, soluvia prefilled microinjection system, has reached the market. the vaccine-device combination product was fda approved in may 2011 for intradermal delivery of fluzone influenza vaccine. we have identified more than 25 companies, with proprietary microneedle technology, actively working towards the development of microneedle-based drug or vaccine products. clearside biomedical, nanopass technologies, corium international, circassia, radius health and zosano pharma are examples of companies which are evaluating microneedle based drug/vaccine – device combination products (referred to as products hereafter) in clinical trials.during the course of our research, we came across 22 products currently in different stages of development. we expect around ten products to be launched by the end of this decade, providing the much needed push to this market. technological advancements will ensure the development of microneedle systems with improved safety and efficacy profile. as more products move from pipeline to the market, we expect to see an increase in the investment in this area from various quarters. scope of the reportthe 'Microneedles for transdermal and intradermal drug delivery, 2014-2030' report provides an extensive study in the field of microneedle based delivery systems for therapeutic use. the report covers various aspects, such as, benefits of microneedle assisted drug delivery over conventional needle-syringe system, key industry stakeholders, manufacturing challenges and upcoming opportunities.one of the key objectives of this

report is to understand the current and future state of the microneedles market. this is done by analysing – products currently available in the market and those under development (both clinical / pre-clinical)- re…”
Tayyaba, S., Ashraf, M. W., Afzulpurkar, N., & Khaleeq Ur Rahman, M.. (2013). Design, simulation and development of gold microneedles patch. In ASME International Mechanical Engineering Congress and Exposition, Proceedings (IMECE)

Plain numerical DOI: 10.1115/IMECE2013-64443
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“Technological advancements are essential for all fields of life particularly in health discipline to test and analyze the biological and biomedical samples. biological micro electromechanical system (bio-mems) based healthcare technologies are handy to make human life comfortable and snug by ease of use, eradicating pain, reducing risk of diseases, improving diagnosis process and treatments techniques. in this study the design, simulation and development of piezoelectricaly actuated microfluidic device (gold needle patch) has been presented. the simulation of skin insertion using gold needle into skin to study the effects of skin piercing and optimize the design of needle has been conducted in ansys autodyne by making 3d model with applied force 0.4 to 0.9 n at the tip area of needle. the microfluidic analysis of 3×3 microneedle patch has been carry out in ansys workbench using computational fluid dynamic (cfx) environment. the maximum velocity 2.015 e4 m/sec has been achieved. after the successful development of gold needles patch, the fluid transport and insertion test of piezoelectricaly actuated patch also has been conducted using chicken skin. copyright © 2013 by asme.”
Chong, W., Teodorescu, M., Martini, A., & Rahnejat, H.. (2012). Mechanisms of entrapment and release of fluid droplets from nano-scale surface features. In American Society of Mechanical Engineers, Tribology Division, TRIB

Plain numerical DOI: 10.1115/IJTC2012-61201
DOI URL
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“Engineering surfaces are never perfectly flat. they contain micro and nano-scale features on multiple length scales. predicting the amount of fluid trapped in these minute surface crevices and its controlled release could benefit a variety of practical applications. in a sliding contact, the released fluid could create an ultra-thin film, reducing the direct contact and consequently the boundary friction. transdermal patches are the least invasive of available subcutaneous drug delivery techniques. the drug is stored in a micro-reservoir and it is released to the skin either through a permeable membrane or through a series of micro needles. the aim of the current paper represents the first attempt to investigate whether a modeling approach encompassing two complementary simulation techniques in an integrated framework can be used to predict the volume of fluid stored in a nano-scale surface feature. molecular dynamics (md) simulation could provide accurate modeling of fluid behavior at nano-

scale, and statistical mechanics (sm) could provide a fast prediction. copyright © 2012 by asme."
Chen, P. C., & Hsieh, S. J.. (2014). 3-D biocompatible microneedle arrays with nanoporous surface. In FAIM 2014 – Proceedings of the 24th International Conference on Flexible Automation and Intelligent Manufacturing: Capturing Competitive Advantage via Advanced Manufacturing and Enterprise Transformation

Plain numerical DOI: 10.14809/faim.2014.0977
DOI URL
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“During the past few years, developing painless needles or patches to replace traditional hypodermic needles has been investigated. since micromachining can be used to construct a high density metallic micropillar array, we propose to use a biocompatible metal oxide, such as al2o3 and tio2, as an alternative material for fabricating arrays of microneedles. in this study, we fabricated an anodic aluminum oxide (aao) covered al micro-indent array using electrochemical and mechanical micromachining. we demonstrate use of a nanoindenter to make pyramidal indentions on al surface in order to produce a female microneedle array mold. we also performed melting injection to fill aao template with ultra-high molecular weight polyethylene (uhmwpe) to produce uhmwpe nanotubes. the microneedle array provides a 3-d structure that possesses several hundred times more surface area than a traditional nanotube template. this suggests that a medical-grade polymer microneedle array can potentially be formed for more applications. this 3-d microneedle array device can be used not only for painless injection or extraction, but also for storage, highly sensitive detection, drug delivery, and microelectrodes.”
Tautorat, C., Koester, P. J., Held, J., Gaspar, J., Ruther, P., Paul, O., … Baumann, W.. (2008). Intracellular potential measurements of adherently growing cells using micro-needle arrays. In 12th International Conference on Miniaturized Systems for Chemistry and Life Sciences – The Proceedings of MicroTAS 2008 Conference

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“We present a new sensor chip system for intracellular potential measurements of adherently growing cells using micro-structured needle electrode (mne) arrays. existing methods for intracellular investigations are time-consuming, tedious or limited to the analysis of suspended cells. however, most biological cells grow adherently. to overcome these methodological limitations a novel technique, local micro-invasive needle electroporation (lomine) in mne arrays, has been developed. lomine opens the cell membrane for introducing a mne into the cytoplasm. this paper describes the fabrication process of the mne-array chips and first cell electroporation experiments.”
Held, J., Gaspar, J., Ruther, P., & Paul, O.. (2008). Microneedle Arrays Electrode With Dielectrophoretic Electrodes For Intracellular Recording Applications. In 6th International Meeting on Substrate-Integrated Micro Electrode Arrays

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“This paper reports on the fabrication of microneedle electrodes for thenelectroporation of adherent cells and intracellular recording applicationsnwith focus on the influence of external factors in cell

metabolism.nclassical methods such as the patch-clamp method have been applied mostlynto single cells in suspension. however, in the human body the majority ofncells are adherent cells, which motivated the development of the newnmicroneedle-based chip design. the chip comprises an array of 64nmicroneedles with each needle combined with two dielectrophoresis (dep)nelectrodes to attract cells towards the needle electrodes. the arraynoccupies a total area of approximately 1 mm2. the microneedles arenfabricated using dry etching of silicon, followed by insulation, twonmetallization and two passivation layers. the passivation layer is openednat the tip of the needles in order to expose the metal for cell positioningnvia dielectrophoresis, electroporation, and intracellular recording.nvarious needles with diameters as small as 1 μm and a height smaller thann10 μm were fabricated. preliminary investigations have shown that heartnmuscle cells, fibroblasts, and also primary cells of mice and rats grow onnthese structures [1].nthe available classical patch-clamp methods for intracellular measurementsnof cells in suspension are time-consuming and require experienced laborn[2]. absolute values of the transmembrane potential vm are between 20 mvnand 200 mv in living cells, depending on organism and cell type [3].nhowever, the absolute measurement of vm is not possible with planarnelectrodes. patch-on-chip systems are presently limited to theninvestigation of suspended single cells [4]. however, adherent cells need anbiological matrix or artificial biocompatible attaching materials on whichnthey can firmly grow. all above-mentioned methods, with exception of thenwhole-cell patch-clamp are limited to the investigation of ion channels. nthe fabrication process of the microneedle electrodes is schematicallynshown in fig. 1. the three-dimensional definition of the microneedlesncomprises three dry etching steps, namely: isotropic, anisotropic andnisotropic silicon etching. the first step realizes the tip of the needle,nthe anisotropic etching step adjusts its height, and the final isotropicnstep thins the needle and sharpens its tip, see fig. 1 (b). by varying thenetch mask diameter and process parameters, different needle profiles can be…”
Lee, J., Jung, J., Shin, D., & Kim, Y. T.. (2012). Patch type sensor module for diagnosis of acute myocardial infarction. In Proceedings of IEEE Sensors

Plain numerical DOI: 10.1109/ICSENS.2012.6411371
DOI URL
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“Myocardial infarction is getting more attention in human health care system by the busy daily activity and prolonged human life span. myocardial infarction is not easy to detect in early stage. whether it is acute or not, it can be chronically fatal without proper detection and treatment in early stage of warning signs. our research is focused on the wearable device that detects myocardial infarction by monitoring cardiac markers from tiny amount of blood sample. our device consist with three parts, blood sampling part, electrochemical sensor part and signal processing part. blood sampling part extracts about 10ul of blood sample with micro-needles, then the blood is transported to electrochemical sensor through polymer parylene coated microfluidic channels. electrochemical sensor detects electro-chemical current generated by oxidation-reduction cycle at the three dimensional integrated micro-electrodes. signal processing part includes traditional signal conditioners such as i-v converter, amplifier and filter, and data processing units such as a/d, d/a convertors and micro-processor. the usefulness of out device is extended by providing combined on line communication capability with bluetooth local area communication and wifi and/or 3g wireless networks. every realtime sensor data and status information from the sensor modules are collected by centralized server located in hospital. with our myocardial infarction diagnosis device, the patients’ unexpected heart attacks can be prevented and the hospital

may provide controllable risk caring for the disease without hospitalization of the patients. © 2012 ieee."
Bavi, N., Cox, C. D., Perozo, E., Martinac, B., Mbengue, M., Navaud, O., … Davis, R. W.. (2015). Special Paper 373. BMC Plant Biology

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"Mechanical stimulations play a significant role in the day to day existence of plants. plants exhibit varied responses depending on the nature and intensity of these stimuli. in this review, we present recent literature on the responses of plants to mechanical stimuli, focusing primarily on those exerted during plant-microbe interactions. we discuss how microbes are able to apply mechanical stimuli on plants and how some plant responses to pathogenic and symbiotic microbes present striking similarities with responses to mechanical stimuli applied, for instance, using micro-needles. we hypothesize that appropriate responses of plants to pathogenic and symbiotic microbes may require a tight integration of both chemical and mechanical stimulations exerted by these microbes. © 2014 elsevier ltd."
Trada, H., Walsh, K., Isham, A., & Cambron, S.. (2007). Out-of-plane micro-needle arrays using silicon micromachining. In Conference Proceedings – IEEE SOUTHEASTCON

Plain numerical DOI: 10.1109/SECON.2007.342933
DOI URL
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"An array of out-of-plane silicon processed micro-needles has been successfully fabricated using relatively simple fabrication techniques. this abstract describes the methods explored to produce 100-element needle arrays (10×10) on a single die. applications of the micro-needles include transdermal drug delivery and tissue delivery (during surgery). two types of needles were fabricated: solid electrode and hollow through-hole. the solid-core micro-needles can be used for painless perforation of the skin layer to increase absorption of drugs through patches. these types are fabricated using only oxidation, dicing and isotropic etching. the hollow versions have more applications for direct delivery of drugs through the skin and require additional steps of lithography and deep reactive ion etch (drie). in both cases, the fabrication process starts with thermal oxidation of a ?100? orientation, p-type, 500ums thick silicon wafer. wet oxidation of the wafer at 1000°c yields an oxide layer of ? 0.5?ms thickness. the wafer is then diced with a diamond blade along the x and y directions. the cuts are spaced 250?ms apart and approximately 350-400?ms deep. this results in square pillar-like structures which are 250?ms in size (on a side) and 350-400 ?ms tall. the cuts are made to yield an array of 100 (10×10) pillars following which, another series of cuts is made to separate the arrays into individual die samples each containing 100 elements. to obtain the hollow needle structures, a drie step is required to create holes in the wafer. this etch step is performed prior to dicing the wafer. the wafer is spin-coated with microchem corporation's negative photoresist su-8 50. this epoxy-based resist gives a layer thickness of about 100 ?ms, which is essential to protect the silicon during this etch. the wafer is patterned using a photomask of arrays of 50?m hole openings. the relatively small lumen size of 50?ms and the etch depth of 500?ms requires a 10-12 hour etch which necessitates the thick protective layer. after the holes are etched, the pillars are cut around the holes such that the hole openings are centered in the x direction and 10?ms off-centered in the y direction. this yields a micro-needle with an off-centered lumen opening. the off-centered opening prevents blockage of the passage during delivery. we

explored both wet chemical and dry gas etching approaches to isotropically etch the standing pillars. the wet etch involves the use of a mixture of 5% hyd…”