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研究課題名（和文）Porous Microneedles filled with an Glucose-responsive Hydrogel for Self-Regulated Insulin Delivery

研究課題名（英文）Porous Microneedles filled with a Glucose-responsive Hydrogel for Self-Regulated Insulin Delivery

研究代表者

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研究成果の概要（和文）：経皮薬物送達には多くの利点があります。 注射や経口投与に比べて非侵襲的であり、消化による薬物の分解が防止されます。 マイクロニードル（MN）は経皮投与として普及しました。 それらは小さな針状の構造で構成されており、アレイパターンで配置されています。 MN は皮膚に小さな穿刺穴を多数作るため、痛みは生じません。 これにより、侵襲性が最小限に抑えられ、薬剤をより効率的に送達することができます。 この研究レポートでは、多孔質 MN のさまざまな材料を調査し、細孔を別の材料で充填しました。このアプローチにより、機械的強度が強化され、優れた薬物送達能力を備えたハイブリッド MN が調製されました。

研究成果の学術的意義や社会的意義
To increase mechanical stability, we permanently filled the pores, a process that has not been done very often in the literature. In addition, this method can prevent clogging of the pores through the absorption of body fluids and a sustained and long-term drug release can be maintained.

研究成果の概要（英文）：Drug delivery across the skin (transdermal) offers a number of advantages. Compared to injections or oral administration it is non-invasive and drug degradation caused by digestion is prevented, respectively. Recently microneedle (MN) became popular for transdermal administration. They consist of a collection of tiny, needle-like structures that are typically less than a millimeter in length and are arranged in an array pattern on a substrate. MN devices create many small puncture holes in the skin whereby little to no pain is caused. This makes them minimally invasive and the drug can be delivered through the holes much more efficiently. MN arrays can be made from different materials and their morphology can be solid, hollow or porous. In this research report we explored different polymeric materials for porous MNs and filled the pores with another gel-like material. By this approach hybrid MNs were prepared with enhanced mechanical strength and good drug delivery capabilities.

研究分野：Biomedical engineering

キーワード：Microneedle　Drug release　Hydrogel　Diabetes　Insulin

１．研究開始当初の背景

The microneedle (MN), a two-dimensional array has recently attracted increasing interest as minimally invasive tool for transdermal drug delivery. A MN patch, which contain sharp needles with length ranging from 25 to 2000 μm, can penetrate skin to bypass the diffusion barrier of the stratum corneum, the outermost layer of skin, and transient microchannels without touching nerve fibers and blood vessels are formed. Therefore, macromolecules (e.g., vaccines or insulin) could be effectively transported across the skin barrier in a pain-free, risk-free and self-administered way. MN arrays can be classified according to their morphology, and recently porous microneedles (PMN) became of interest as they are advantageous for fast liquid absorption and drug release. Polymers as a porous material have been applied and they possess good biocompatibility, increased permeability, tunable molecular weight, and facile fabrication processes like molding and UV-polymerization. Nonetheless, a sustain and long-term drug release through the microchannels of a PMN is still challenging. PMN pose the risk of breakage and leave the debris of needles underneath the skin and inflammation of the tissue can happen. Moreover, cloggage of the pores by body fluid absorption could result in discontinuity of the drug flow. A denser network structure is one approach to increase the mechanical strength; however, this usually result in less porosity and a reduced permeability of the material. On the other hand, increased permeability could be achieved by higher porosity resulting in a more fragile material

２．研究の目的

PMN contain a large network of interconnected pores, which enables efficient fluid transportation into and from inside the skin. They are, however, intrinsically fragile because of a large volume of the void.

Our approach was that the interplay of a scaffolding polymer material and a soft hydrogel material could provide both increased mechanical stability and efficient drug release ability. By this method hydrogel-filled porous microneedles (FPMN) are formed which could significantly improve the sustain and long-term drug release after skin penetration.

３．研究の方法

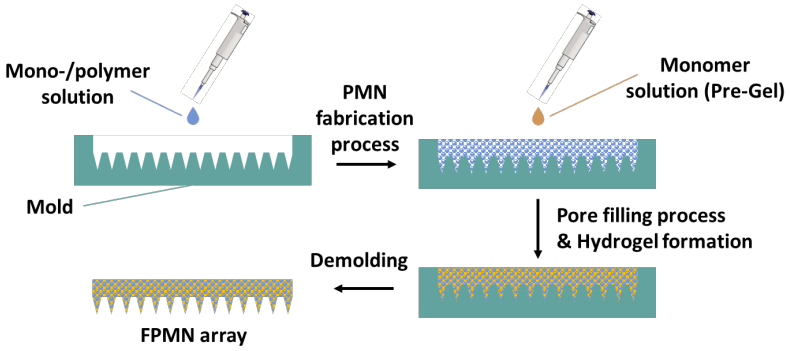
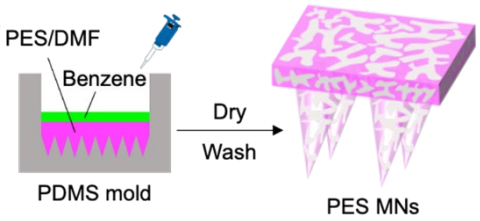


Figure 1. Schematic representation of the FPMN fabrication process.

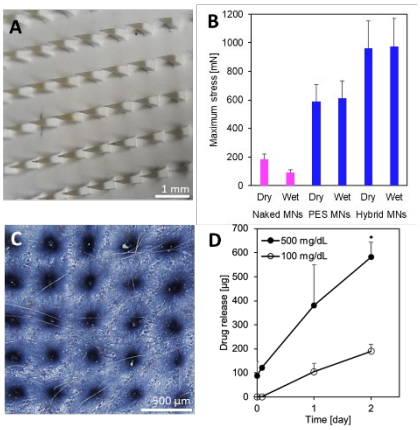
FPMN arrays were prepared in two steps. At first porous microneedles (PMN) arrays consisting of a stable, non-biodegradable polymer material with high porosity was produced by different reported PMN fabrication processes (Figure 1). The readily prepared, μm-size pores will be subsequently filled by soaking them with another monomer solution. The porous material absorbed the liquid quickly and polymerization was performed afterwards to produce a permeable hydrogel network within the pores. Before and after the filling process the mechanical stability of the MN array was investigated by shear stress-strain tests and in vitro skin punctuation tests. The filled MN array was investigated by their insulin release ability as a self-autonomous medication for diabetes mellitus patients. Moreover, the hydrogel contains a glucose-sensing element which can control the release of insulin by changing the permeability at different glucose levels.

４．研究成果

(1) Poly(ether sulfone)-based PMN arrays



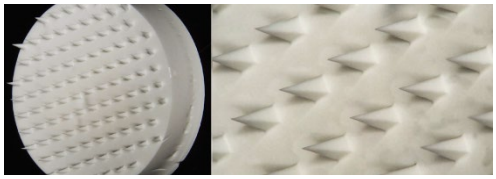
We have investigated commercially available poly(ether sulfone) (PES) as a polymeric material for the PMN fabrication. PDMS molds were filled with a PES solution in DMF and benzene was added on the backside of the solution. The benzene diffuses slowly into the solution and can interact with the aromatic rings of PES by pi stacking. The PES solution solidified overnight and was subsequently washed by methanol to remove the intercalated benzene. By this method, μm-size pores remain in the polymer structure, whereby the PES and benzene concentration are crucial parameters for a good MN morphology and control of porosity. Since PES is a hydrophobic polymer, plasma treatment and surface coating by poly(acrylic acids) was applied to facilitate pore filling process by the hydrophilic pre-gel solution. The pre-gel solution contains a mixture of various acrylate-based monomers, crosslinker and initiator in methanol and was added on the backside of the PES MNs. The solution was soaked in by capillary force and could be thermally polymerized afterwards (i.e., gelation process).



The morphology of the novel hybrid MNs was confirmed by optical microscopy showing sharp and uniform needles (Figure A). The mechanicals strength was investigated by shear stress-strain tests of a single microneedle. It was shown that the maximum stress in the PES MNs was significantly higher than the dry or wet MNs consisting of only hydrogel (i.e., naked MNs) (Figure B). Moreover, the mechanical strength increased from around 0.6 N (PES MNs) to 1 N (hybrid MNs) which clearly shows the reinforcement effect by the pore filling process.

The hybrid MNs were analyzed in vitro by skin punctuation test. It was shown that the new material could efficiently penetrate the stratum corneum of mouse skin. A uniform microchannel formation was confirmed by trypan blue staining (Figure C). The glucose-responsive insulin release was analyzed by immersing the hybrid MNs in a fluorescein isothiocyanate-labeled (FITC) insulin solution overnight, whereby the hydrogel absorbed the insulin. Subsequently, the insulin soaked MNs were immersed buffer solution with different amount of glucose. The hydrogel can interact with glucose and the resultant change in counterionic osmotic pressure translates into a change in the hydration state of the gel. A localized dehydration of the gel surface occurs and forms a so-called “skin layer” which enables release of insulin from the gel. The released amount of FITC insulin in the buffer solution was estimated by fluorescence spectroscopy and it could be shown that the hybrid MNs still show the glucose concentration-dependent release profile (Figure D).

(2) Cellulose acetate-based PMN arrays



One major drawback was the hydrophobicity of the PES, thus, we have investigated cellulose acetate (CA) as a more hydrophilic material. The arrays were made by diffusion of water into solution of CA in DMSO. The slow exchange of the solvents results in precipitation of the polymer and after optimization of the conditions, sharp and uniform microneedles could be formed. The needles featured very high porosity (~90%), narrow pore size (~2 μm) and moderate mechanical strength (~0.2 N).

Since CA is more hydrophilic material it could easily absorb our pre-gel solution (mixture of monomer solutions). The hydrogel was formed in the interconnected pores after UV-polymerization of the monomer soaked PMN array. Unfortunately, the mechanical strength did not increase significantly after the filling process. Moreover, FITC-insulin release studies only showed poor glucose concentration-dependent release and further optimization need to be done.

５．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計2件（うち招待講演　0件／うち国際学会　0件）

１．発表者名 松元 亮, Siyuan Chen, 宮崎 拓也, 伊藤 美智子, Barthelmes Kevin, 松本 裕子, 金井 紗綾香, 池原 清, 諸岡 由佳, 木村 慎一郎, 田中 都, 菅波 孝祥, 宮原 裕二
２．発表標題 高分子ゲルの階層的エンジニアリングによる持続型マイクロニードルデバイスの開発
３．学会等名 第70回高分子討論会
４．発表年 2021年

１．発表者名 宮崎 拓也、Barthelmes Kevin、池原 清、宮原 裕二、松元 亮
２．発表標題 力学的強度と薬剤放出能を両立させるスマートゲル内包多孔質マイクロニードルの設計と評価
３．学会等名 第33回高分子ゲル研究討論会
４．発表年 2022年

〔図書〕　計0件

〔出願〕　計1件

産業財産権の名称	発明者	権利者
薬剤送達デバイスおよびその製造方法	松元 亮、宮崎 拓也、Barthelmes Kevin、池原 清	同左
産業財産権の種類、番号	出願年	国内・外国の別
特許、2021-144286	2021年	国内

〔取得〕　計0件

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関