Institution: Swansea University

Unit of Assessment: 8

Title of case study: Improving microneedle manufacturing efficiency and developing a product pipeline in a leading microneedle technology company

Period when the underpinning research was undertaken: 2011 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Owen Guy	Professor	2001-Present
Sanjiv Sharma	Lecturer	2017- Present
Natalie De Mello	Research Associate	2014-2018
Chris Philipps	Lecturer	2009-Present

Period when the claimed impact occurred: August 2013 – December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

The research of Prof. Guy at Swansea University (SU) has been instrumental in the commercial success of Innoture Ltd, a leading microneedle (MN) company, focusing on their novel anti-aging regime Radara®, using microneedle patches, with generated sales of GBP50,000 in 2020 even with retail outlets closed due to COVID. Research conducted by Swansea researchers allowed the company to optimize their MN print manufacturing processes, making production more efficient and faster and bringing Radara® products to market 1 year earlier than planned. Swansea-developed microstructure prototypes for transdermal delivery have also allowed Innoture to develop a new product pipeline around analgesics, with Swansea facilitating the first human trials for the company. Critically, Swansea University research has underpinned Innoture's ability to secure investment funding of GBP3,000,000 during the REF period, allowing the company to add 12 staff, an increase of 600% from 2014.

2. Underpinning research

Microneedles (MNs) that penetrate the top layer of the skin have long promised pain-free administration of drugs, but, despite a plethora of research publications, very few have ever approached commercial reality. Scalability of production, drug yield and molecular size/type (solubility) have severely limited MN application. Professor Guy's research has effectively solved these issues by providing the underpinning knowledge needed to deliver small molecules and complex biologicals (peptides and cells) at high volume from mass-manufacturable printed patches (Fig. 1). His work represents a step change in MN patch technology that has since seen commercial exploitation via a 7-year collaboration with Innoture Ltd - taking the technology from manufacture to successful human trials.

Since 2011, **Guy** has been developing a range of MN fabrication technologies for silicon and polymer MNs in collaboration with industry and Imperial College London (Sharma PI). Innovations in microneedle design (pitch, length, tip sharpness and material hardness) have enabled facile transdermal injection leading to a critical process patent for the manufacture of MNs [**P1**]. A key element was a novel "bevelled tip" hollow MN, which led to new collaborations with Prof. Birchall's group at Cardiff University. **Guy** has led EPSRC [**G1, G2**] and InnovateUK [**G3**] MN projects with Cardiff developing the MN technology for transdermal delivery of large fluid doses [**R1**].

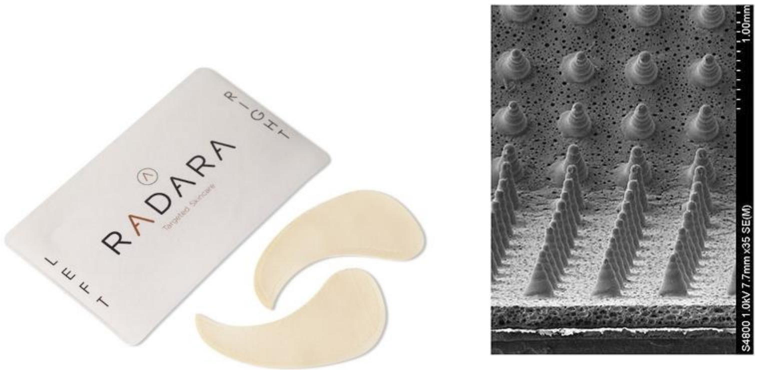

Fig.1. Radara® patches (left) and electron micrograph of microneedles (right)

Given Swansea's leading expertise in MN manufacturing, characterisation and skin-testing research, through Swansea's Centre for Nanohealth (CNH, of which Guy is a co-director), **Guy** initiated a Knowledge Transfer Partnership (KTP) collaboration with Innoture in 2013 [**G4**]. Key research outcomes arising from this KTP were the development of novel MN manufacturing processes for screen-printed polymeric microneedle patches [**R2, R3, R4**]. SU's critical input [**R2, R3**] included the development of screens, ink constitution and viscosity, ink curing and substrate selection leading to MN optimisation. [**R2**] detailed how a newly developed bend test was an excellent predictor of amount of ink deposited and was far better than traditional assumptions based on squeegee hardness. The printing of microneedles relies on a different philosophy from traditional printing, where excess ink deposition is regarded as wasteful. Microneedle printing is pushing the screen-printing process to the limits of its capabilities in terms of the amount of material deposited.

In [**R3**] we visually showed for the first time the separation of the ink filament as the stencil is pulled away from the substrate. This study is of great importance to the functional printing industry as it is the first time that frequently cited and historical models of the ink transfer process in screen printing have been tested and validated experimentally. This allows a direct causal link to be drawn between ink characteristics (elasticity, rheology) and printer settings, and print topography, based on the simultaneous contact between the printing form, ink and substrate. Understanding of printing mechanisms, and the effect of process parameters, is key to ensuring defect free and robust manufacture of printed microneedles as well as maximising ink deposit for faster throughput.

Prof Guy has led research into the testing and development of MNs in association with active pharmaceutical ingredients (APIs) [**R4**]. This involved skin testing research and new methods for assessing transdermal delivery of commercially relevant APIs (ibuprofen, aspirin and hydrocortisone, galantamine, selegiline hydrochloride (Sel-HCl), insulin and caffeine [**R4**]). Key characterisation and performance data on Innoture's MNs (skin penetration and drug permeation efficacy) were acquired, with the study providing critical data on the effect of a molecule's physiochemical properties on its ability to be delivered transdermally, with and without microneedle application. Enhanced delivery of APIs has been demonstrated in **De Mello's** work (via extended KTP, [**G5**]), with the avoidance of hypodermic needle stick pain during anaesthetic administration into the gums of dental patients.

Prof Guy's group in CNH has conducted research into materials characterisation, microneedle sensing (including the first mediated MN based biosensor for minimal invasive sensing of lactate in interstitial fluid [**R5**]) and examined the possibility of developing a MN closed loop control system for delivery of precision drugs [**R6**]. Most recently, this technology has been used in the development of a "vaccine smart patch" – for COVID vaccination and diagnosis of COVID antibodies in response to the vaccine.

3. References to the research

All underpinning papers and grants have been peer reviewed, with 3 papers in Q1 journals (JCR 2019). Five papers were supported by external funding sources including Innovate UK, Trelleborg, Welsh Government, NRN, EPSRC and the Italian Research Council. This research has made important contributions to the microneedle technology internationally and contributes important knowledge to the field likely to have a lasting influence.

[R1]. Gualeni, B., Coulman, S.A., Shah, D., Eng, P.F., Ashraf, H., Vescovo, P., Blayney, G.J., Piveteau, L.D., Guy, O.J., Birchall, J.C. (2018) Minimally-invasive and targeted therapeutic cell delivery to the skin using microneedle devices. British Journal of Dermatology 178:731–739. https://doi:10.1111/bjd.15923

[R2]. Phillips, C.O., Beynon, D.G., Hamblyn, S.M., Davies, G.R., Gethin, D.T., Claypole, T.C. (2014) A study of the abrasion of Squeegees used in screen printing and its effect on performance with application in printed electronic. Coatings 4:356-379. https://doi:10.3390/coatings4020356

[R3]. Potts, S. J., Phillips, C., Jewell, E., Clifford, B., Lau, YC., Claypole, T (2020) High-speed imaging the effect of snap-off distance and squeegee speed on the ink transfer mechanism of screen-printed carbon pastes. Journal of Coatings Technology & Research 17:447-459. https://doi.org/10.1007/s11998-019-00291-6

[R4]. Rahbari, R., Ichim, I., Bamsey, R., Burridge, J., Guy, O., Bolodeoku, J., Graz, M. (2020) Characterisation of Drug Delivery Efficacy Using Microstruture-Assisted Application of a Range of APIs. Pharmaceutics 12:1213. https://doi.org/10.3390/pharmaceutics12121213

[R5]. Bollella, P., Sharma, S., Cass, A., Antiochia, R. (2019) Microneedle-based biosensor for minimally-invasive lactate detection. Biosensors and Bioelectronics 123:152159. https://doi:10.1016/j.bios.2018.08.010

[R6] Howells, O., Rajendran, N., McIntyre, S., Amini-Asl, S., Henri, P., Liu, Y., Guy, O., Cass, A.E.G., Morris, M.C., Sharma, S. (2019) Microneedle Array-Based Platforms for Future Theranostic Applications. ChemBioChem 20:2198-2202. https://doi:10.1002/cbic.201900112

Grants

[G1]. Guy, O., (PI), Summers, H., (CoI), Birchall, J., (CoI), Coulson, S (CoI). (05.2014-11.2016). Manufacture of silicon microneedles for drug & vaccine delivery. EPSRC, [EP/L020734/1] GBP564,437

[G2]. Guy, O. (PI) (10.2010 - 09.2012). Ultra-sensitive graphene nano-biosensors. EPSRC, [EP/I00193X/1], GBP101,163

[G3]. Guy, O., (Swansea PI), Birchell J.P. (Project PI). (09.2013-05.2016). Precise cell therapy using minimally invasive microneedle devices. Innovate UK [TS/L001640-1], GBP250,000 (GBP75,000 Swansea University)

[G4]. Guy, O., Innoture Ltd. (01.2014-12.2014). sKTP 1000919. Innovate UK and Welsh Government, GBP64,900

[G5]. Guy, O., Innoture Ltd. (08.2016 – 07. 2018) KTP 10473. Innovate UK and Welsh Government, GBP149,500. (N. De Mello was the associate on this KTP).

Patent

[P1]. Liu, Y., Guy, O.J. (2015) Manufacture of microneedles. US20160264408 A1, EP3060290A1, WO2015059437A1, https://bit.ly/37L1Het

4. Details of the impact

Improved manufacturing processes/cost efficiencies

Swansea University's microneedles research underpinned Innoture's development of the world's first cosmetic MN patch product, Radara®, in late 2015 [**C1, C4**]. SU's research on the MN printing process and skin testing of MNs has allowed Innoture to branch into an entirely new business sector (non-surgical cosmetic and therapeutics) through their Radara® products, worth GBP50,000 in 2020 [**C1**].

"*Screen-printing research at Swansea University was key to developing Innoture's ability to print MNs in large volumes (5,600 Radara patches per day) and at low cost, allowing us to reduce manufacturing costs by 50%"* [**C1,** Head of Research, Innoture Ltd].

Additionally, advances in ink and polymer development, polymer curing, iterative printing process and tip sharpening allowed the company to develop a super-fast, large volume, screen-printed MN production process for Radara – establishing a new production line in 2016. Using Swansea's processes has saved the company over GBP1,000,000 since 2014 compared to using other commercial facilities [**C1**].

Swansea University's skin testing research has helped Innoture optimise their Radara® patches, contributing to the launch of the first and second versions of the micro- channelling patches a year ahead of schedule "*which allowed the company to double its turnover from 2018 to 2019"* [**C1,** Head of Research, Innoture Ltd,].

A new variation of Radara® for the total eye area is the latest high-performance eye rejuvenation offering from Innoture and has been developed using SU research (MN development and hyaluronic acid permeation characterisation).

"In just two years (2014-2016), we've seen Radara®, our novel anti-ageing regimen using unique micro-channelling patches, go from a technological concept to an award-winning skin care brand (e.g. Best Home Use Product of Device category, My FaceMy Body Awards 2016), only with the input of Swansea University research" [**C1**, Head of Research, Innoture Ltd, also see **C3** for award example].

New product development

"Prof Guy and his colleagues at Swansea University have led the way in developing MSt fabrication processes, characterising our MSts, facilitating clinical trials for our products and allowing us to develop a product pipeline incorporating Active Pharmaceutical Ingredients (APIs)" [**C1,** Head of Research, Innoture Ltd].

Innoture's proprietary platform has the capability to deliver small molecules, peptides and complex biologicals though a MN patch (less than 1ml). The ability to deliver large molecules (above 1ml) is a step change in transdermal patch technology. SU research has investigated delivery of some larger molecules, including hyaluronic acid and APIs (ibuprofen, lidocaine) with MNs, starting in 2016.

The foremost pipeline development products are MN pain-relief patches containing ibuprofen and lidocaine. Transdermal drug delivery research performed by SU under the 2016 KTP was critical in developing MN coatings and drug encapsulation processes for delivery of pain relief APIs (lidocaine and ibuprofen) using a MN platform and in validating prototype pain-relief patches. We were given approval by the MHRA to run a clinical investigation in 2018 to assess the performance of Lidocaine with a MN patch. The results showed a significantly enhanced delivery of APIs over current treatments.

SU developed all skin testing protocols and facilities (Guy and De Mello), gaining full ethical approval for research on animal and human skin in 2016. This allowed Innoture's first successful submission to the Medicines and Healthcare products Regulatory Agency (UK) for a clinical evaluation for a pharmaceutical application. The KTP research project with SU also successfully demonstrated a dental product via a clinical trial (trials conducted at Bristol University in 2018, ClinicalTrials.gov Identifier: NCT03629041).

SU's research has enabled the design and delivery of a new prototype microstructure patch for drug and vaccine delivery and combining diagnostic sensors with vaccines [**C5**], particularly for viral pathogens such as influenza and COVID-19. Already, this research has attracted GBP290,000 in grant funding [**C5, C6**].

Company Impact

SU's research has directly impacted Innoture's ability to attract investment, expand Innoture's workforce and increase Innoture's share price from GBP8 to GBP20 (2016 to 2019) [**C1**].

Innoture secured investment funding of GBP1,000,000 in 2014-16 and GBP2,000,000 in 2017-2020 [**C1**]. SU data (SEM, ethically approved skin testing, mechanical tests, clinical trials data and regulatory approvals) and optimization of manufacturing processes. undertaken by Prof Guy's research team, were critical in securing this investment and in the subsequent scale-up and launch of Innoture's commercial products.

The Radara® patches have been advertised to a global audience through publications such as VOGUE, Harper's Bazaar, Cosmopolitan and Tatler (see [**C2**] for example) and is now available through selected retailers, skin care institutes and clinics such as national chain SK:N and Church Pharmacy. Revenues from current Radara® products have risen from GBP10,000 in 2016 to GBP50,000 in 2020 [**C1**]**.**

Employment

Since 2014, the number of employees at Innoture has increased from 2 to 14.

"We have been able to grow our workforce by 12 since 2014 – an increase of 600% - including employing Swansea University chemistry and engineering graduates, as a direct result of the development of our product pipeline which has grown with Swansea university research input" [**C1,** Head of Research, Innoture Ltd,].

5. Sources to corroborate the impact

[C1]. Innoture Ltd testimonial letter–Head of Research

[C2]. Confirmation of product release and coverage in the national press: https://bit.ly/3qLqXYz

[C3]. Confirmation of award-winning Radara® product: http://radara.co.uk/2016/12/15/radara-wins-face-body-award-best-home-use-product/ ,

http://radara.co.uk/2016/12/15/radara-commended-aesthetics-awards-innovative-product/

[C4]. Confirmation of research relationship with SU: http://www.innoture.co/about-us.htm

[C5]. Confirmation of product release and coverage in the national press: https://www.sciencefocus.com/news/covid-19-vaccine-smart-patch-uk/

[C6]. Confirmation of research on skin patch for COVID vaccines https://bit.ly/3vkEGcp