

Impact case study (REF3)

Institution: University of Warwick		
Unit of Assessment: B8 - Chemistry		
Title of case study: New medical adhesives for transdermal drug delivery – Medherant Ltd		
Period when the underpinning research was undertaken: 2014 – 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:
David Haddleton	Professor of Chemistry	1993 – Present
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact (indicative maximum 100 words)		
<p>A new class of thermoset moisture-curing solvent-free pressure-sensitive adhesives (PSAs) has been developed for innovative applications in transdermal drug delivery. Innovation is demonstrated in several areas: solubilisation of pharmaceuticals as their native free acids or bases (rather than their salts) giving significantly higher drug loadings and more efficient systemic delivery than for conventional PSAs; enhanced hydrogen-bonding in the urea based adhesives improving adhesion, even with perspiration and bathing. The 3D network removes disadvantages arising from cold flow (whereby the adhesive flows undesirably outside of the area of the backing on wear). The spin-out company Medherant Ltd was established by Professor David Haddleton to exploit this disruptive technology giving an efficient route to the clinic for drug-delivery devices for applications including pain relief, smoking cessation and treatment of central nervous system disorders, such as Alzheimer's, supported by multiple funded feasibility studies in partnership with global pharmaceutical companies. Medherant has to date received GBP11,400,000 investment, presently employs 16 staff and has successfully taken a non-steroidal anti-inflammatory drug patch through Phase 1 clinical trials.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Haddleton has over 25 years' experience of fundamental chemistry, development and commercialisation of pressure sensitive adhesives in medical applications. This includes (i) successful commercialisation of hydrogel based PSA ECG and defibrillation electrodes; (ii) development of hydrogel PSA sweat collection skin-adhering devices with Unilever for use in personal care applications [3.1]; and (iii) development of hydrogel antibacterial wound dressings, to combat <i>so-called</i> super-bugs [3.2]. Based on this extensive experience, in 2014 Haddleton realised the potential of a family of moisture-curable poly(ether urethane/urea silicone) PSAs for use in transdermal drug delivery. These PSAs offered several benefits over existing materials: (i) their composition allows for higher loadings and higher transdermal diffusion rates, increasing the systemic flux leading to reduced patch sizes; (ii) removal of solvents from the manufacturing process; and (iii) eliminating undesirable cold flow.</p> <p>This family of urethane PSA's was initially in-licensed with an exclusive global licence from Bostik, for use in medical applications and transdermal delivery; this license was secured partly by Bostik's confidence in Haddleton's track record in the commercialisation of medical adhesives. Professor Haddleton and colleagues at UoW carried out a number of drug diffusion experiments with drug excipients designed to increase transdermal efficiency. The favourable data from the experiments led to the rapid formation of Medherant Ltd. Medherant was immediately located in bespoke purpose-built laboratories on the University of Warwick Science Park to ensure the most efficient route to maximum impact, under the continued scientific supervision and direction of Haddleton. Rapid initial funding was secured from an established venture capital trust (VCT),</p>		

Mercia Technologies Plc., who have continued to support Medherant via both VCT (Enterprise Investment Scheme) and balance-sheet funding.

Haddleton has subsequently invented a range of novel PSAs with improved manufacturing and use advantages over the original in-licensed materials [3.3, 3.4, 3.5]: including use of renewable polycarbonate polyols [3.6], radiation-cure manufacturing [3.7] and development of a new polyurea-based adhesive where hydrogen-bonding properties remove the requirement for added 'tackifying resins' – achieving superior adhesion in a cleaner, simpler process [3.8]. All recent products (post 2019) use this new class of polyurea-based PSAs. These new inventions from Haddleton have led to in-house manufacturing, previously carried out in France, of these proprietary PSAs which have now entered the supply chain under appropriate quality control measures supplied from Medherant directly to the Good Manufacturing Practice (GMP) manufacturing partner for clinical materials production. All pre-clinical manufacturing of both PSA and finished patch is now based in Medherant's facility in Coventry, since mid-2020.

The new PSAs incorporate active pharmaceutical ingredients (APIs) as both free bases and acids (rather than salts), allowing for higher drug loadings than market alternatives leading to increased systemic flux rates and flux duration allowing for patch application for up to 7 days (important in applications such as Alzheimer's). These patches release higher total amounts of API due to reduced interactions between API and PSA as often adhesives used in transdermal applications are charged e.g. contain acids which form salts with the APIs – important in combating drug abuse from used recycled patches (e.g. opioids/Fentanyl). Out of ~40 drugs currently delivered in transdermal patches/topical gels, and an additional ~50 drugs currently administered orally, >75% have been found to be suitable for transdermal delivery using the new PSAs. Around 50% of the drugs that are currently used in topical/transdermal creams are not currently available in patches; mainly as no one has solved how to dissolve them in current commercial adhesives to give the required flux across the skin. Haddleton showed that the majority of these drugs do dissolve in the new adhesives, making them suitable for transdermal delivery. Data has been collected using a patented high-throughput diffusion testing instrument designed by Haddleton and constructed in the Department of Chemistry at Warwick [3.9].

The new patches have been shown to be comfortable to wear, leave no residues, are removed easily and can stay adhered for multiple days, withstanding normal day to day activities. These adhesives out-perform many commercially available products in terms of adhesion, API flux, comfort and cold flow. The underpinning research showed that patches can be loaded with up to 30% (w/w) of some API's (e.g. Lidocaine) with little reduction in skin adhesion; even at 30% drug loading, adhesion can be up to 100x better than current commercial transdermal patches [3.5].

Haddleton serves as Chief Scientific Officer of Medherant, and as a Board director: he has overseen production, scientific and technical teams in Medherant throughout the period.

3. References to the research (indicative maximum of six references) **Warwick = Bold**

Six published patent families covering the PSA used at Medherant have been filed by Professor Haddleton to date (3.3-3.4, 3.6-3.9).

[3.1] Khoshdel, Ezat, Bates, Susan, **Hand, Rachel A., Haddleton, David M.**, Kirby, Gavin W. *Method of capturing stabilising thiols*, WO2019201787. Publication date 24.10.2019, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019201787&cid=P21-KKWMLU-90211-1>

[3.2] **Zhu, Chongyu**, Jinxin, Zhao, **Kempe, Kristian, Wilson, Paul**, Wang, Jiping, Velkov, Tony, Li, Jian, Davis, Thomas P., Whittaker, Michael R. and **Haddleton, David M.** (2017) *A hydrogel based localized release of colistin for antimicrobial treatment of burn wound infection*. *Macromolecular Bioscience*, 17 (2). 1600320. doi:[10.1002/mabi.201600320](https://doi.org/10.1002/mabi.201600320)

[3.3] **Haddleton, David.**, Goubard David and O' Driscoll, C., WO2017077284A1, *Drug delivery containing silyl polymers*. Publication date 11.05.2017, <https://patents.google.com/patent/WO2017077284A1/fi>

[3.4] **Haddleton, David**, WO2018203048; PCT/GB2018/051142, *Drug delivery compositions (excipients)*. Publication date 08.11.2018, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018203048>

[3.5] Tombs, Emma L., Nikolaou, Vasiliki, Nurumbetov, Gabit and **Haddleton, David** (2018) *Transdermal delivery of Ibuprofen utilizing a novel solvent free pressure sensitive adhesive (PSA): TEPI® technology*. Journal of Pharmaceutical Innovation, 13(1), pp.48-57, doi:[10.1007/s12247-017-9305-x](https://doi.org/10.1007/s12247-017-9305-x)

[3.6] **Haddleton, David**, GB2562070A. *Drug delivery composition (polycarbonate – patch)* Publication Date 07.11.2018, <https://tinyurl.com/yxc2ebju>.

[3.7] **Haddleton, David**, P533317/GB1811833.1 (WO2020/016582A1), *Patch (radiation cure)*. Publication date 23.01.2020, [WO2020016582 PATCH \(wipo.int\)](https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020016582)

[3.8] **Haddleton, David**. P534533/GB1811834.9 (WO2020/016581A1), *Patch (amines)*, Publication date 23.01.2020, [WO2020016581 PATCH \(wipo.int\)](https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020016581)

[3.9] Nurumbetov, Gabit, **Haddleton, David**, Tombs, Emma, Nikolaou, Vasiliki, Davis, Nigel. WO 2018154306; 1702956.2, PCT/GB2018/050464, *Diffusion test system (Franz Cell System)*, Publication date 30.08.2018, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018154306>

4. Details of the impact (indicative maximum 750 words)

Medherant Ltd was founded in 2014 to facilitate commercialisation of new drug-delivery technology based on PSA drug-delivery patches developed at Warwick [5.1]. The global Transdermal Drug Delivery (TDD) system market was worth >USD30,000,000,000 in 2015 and is projected to double by 2024. It is driven by the increasing prevalence of chronic diseases, where conventional drug delivery systems have lower potency due to hepatic first-pass metabolism. A significant contributor to market growth is the increasing inclination of both patients and physicians towards pain-free effective drug delivery whilst maintaining constant drug concentrations within their therapeutic window.

Medherant has received GBP11,400,000 investment to date, enabling two successful European Phase 1 clinical trials in August 2018 [5.2] when the company's projected value was GBP15,000,000. Medherant has generated employment for between 15-20 people since 2015, and currently employs 16 staff with approximately half of these scientists [5.2]. Recognition of Medherant is seen through winning the Coventry Telegraph's *Excellence in Science and Technology Award*, 2017, being listed in *The Times Best Places to do Business*, 2020 [5.3] and receiving widespread media coverage in the national and international press [5.4].

The company has developed a business model whereby it develops its own products which it takes through clinical trials, requiring significant medium-term investment for investor return on a 5-10-year time scale, and partnerships with pharmaceutical companies to develop products on a fee-for-service model for short-term and long-term income generation, including future royalty payments. Medherant expects a flotation/trade sale of >GBP100,000,000 by Q4 2021/Q1 2022, with a further Series A investment planned in 2021 for >GBP5,000,000, to move the company to Phase 3 clinical trials readiness. The CEO of Mercia Technologies Plc, an AIM-listed investment group which has invested GBP7,700,000 in Medherant since 2015, states that it is the “*versatility, breadth of technology and leading wisdom in adhesive polymer chemistry that supports our continued belief in the medium to long term potential of the business. Within Mercia’s proprietary*

portfolio of circa 20 investments, as of 31 March 2020, Medherant was by value the fourth largest holding overall and second within its Life Sciences portfolio.” [5.5].

Medherant was awarded an Innovate UK 'Medicines in Manufacturing' grant in October 2018 [5.6]. It designed and installed its own patch manufacturing facility in Coventry in 2018, and successfully produces non-GMP and pre-clinical patches under its own quality control management being supplied directly to GMP FDA-approved manufacturing facilities at Adhex Pharma in Dijon, France. A proprietary patent-protected high-throughput permeation assessment process rapidly identifies formulations to meet target drug release profiles, enabling the development of candidate patch formulations for companies in approx. 2-3 months [3.9]. Medherant has also produced its proprietary TEPI® TDD patches for third parties interested in assessing the suitability of the TEPI® technology for their own drugs. The Innovate UK grant [5.6] allowed Medherant to successfully extend its pilot scale and non-GMP manufacture and early-stage commercial manufacture throughout 2019 and 2020.

Engagement with Pharmaceutical Companies:

As of December 2020, Medherant has undertaken multiple feasibility studies generating GBP590,000 in revenue with global pharmaceutical companies; [text removed for publication] and Cycle Pharmaceuticals [5.2]. [text removed for publication]. In May 2020, Cycle Pharmaceuticals signed an agreement worth [text removed for publication] with Medherant to develop and commercialise multiple products using the TEPI Patch® technology with the aim of delivering best-in-class drug treatments for rare metabolic and neurological genetic conditions, which are under-served diseases in the patient community [5.7]. [text removed for publication] [5.7].

In Q4 2020 Medherant began discussions with [text removed for publication] about potential licensing of its in-house developed diclofenac product for treatment of arthritis. In addition, Medherant has been engaged with [text removed for publication] for pain relief, [text removed for publication] for central nervous system products, dementia and smoking cessation, [text removed for publication] for further pain relief patches for distribution in France, Germany, Belgium and The Netherlands markets, [text removed for publication] for pain relief. Medherant has a marketing deal with a leading UK supplier of cannabidiol (CBD) products who will be marketing Medherant-Coventry manufactured CBD patches for health and well-being in Q2 2021, initially available online with subsequent release in major UK retail outlets, including leading supermarkets.

Indicative Sales Projections:

Smoking cessation patches - Varenicline tablets (Pfizer) for smoking cessation currently generate USD1,100,000,000 revenue (Pfizer's 8th largest revenue generating drug) and will be off patent in 2021/2022. The global market for smoking cessation products is expected to reach USD64,000,000,000 in 2026 growing at a Compound Annual Growth Rate of 16.9% during 2018-2026 (Businesswire, 2020) due to the expansion of Medicare in the US. Smoking remains the single largest preventable cause of death and disease in the US (~5,000,000 deaths/year): Varenicline is the most effective way to reduce and eliminate smoking and this has given Medherant confidence to progress Varenicline TDD patches in Canadian/US clinical trials in Q1 2021 with a USD800,000 contract with AltaBiosciences in place. Medherant has chosen the US for product launch due to the size of the market, the wide acceptance of Varenicline, and the attractive revenue which will allow for continued growth and removal of reliance on investment funding. IPO market research with US-based physicians shows that 60% anticipate the need for a patch to be high and Medherant can expect 40% market share. This will be the first patch to market and is the basis for the planned flotation in late 2021, with revenues forecast to exceed USD300,000,000 per year [5.2].

Pain relief patches – In the UK pricing ranges from GBP2/patch (Salonpas) to GBP18/patch (CBD), with Voltarol and Ibuprofen patches costing ca GBP5/patch. The manufacturing cost of one patch is approximately 5p. There is currently no topical Ibuprofen formulation available in the USA (it is not yet FDA-approved) and Medherant is currently arranging an auction for the rights to their Ibuprofen patch in the US. The market for Lidocaine local anaesthetic patches, in the USA is valued at approximately GBP2,000,000,000 per annum with Lidocaine now being allowed over

the counter as well as via prescription. Medherant have developed a superior Lidocaine patch with a potentially simple route through US clinical trials, which is currently being evaluated by [text removed for publication]. Medherant is also developing cannabinoid delivery patches (both CBD and THC (tetrahydrocannabinol) in regions where cannabinoid use is now legalised for a range of medical uses.

Impacts arising from patch use:

Patches result in improved healthcare outcomes and better quality of life for users globally. The delivery of NSAIDs (non-steroidal anti-inflammatory drugs) transdermally, as opposed to orally, is expected to reduce the number of patients suffering from gastrointestinal (GI) damage which can be caused by prolonged oral dosage of NSAIDs. Patches lead to improved drug delivery for the easier treatment of diseases such as Alzheimer's/dementia. The Medherant 7-day patch under development using the polyurea-based adhesives will allow carers to administer a weekly patch for patients, as indicated by the market research from prescribing doctors in the US and the UK.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] Medherant company website <https://www.medherant.co.uk/>

[5.2] Statement from Medherant CEO plus article, Medherant announces successful study of first transdermal patch, 05.11.2018, <https://www.epmmagazine.com/news/medherant/>

[5.3] Coventry Telegraph Excellence in Science & Technology Award SME of the Year in 2017 (<https://tinyurl.com/4cucschx>), 23.11.2017, plus listing in The Times Best Places to do Business 2020 (<https://tinyurl.com/fd33hxw7>), 09.02.2020.

[5.4] Several (>500) press cuttings in UK and foreign newspapers, for example: Daily Mail, Could this finally end the agony of back pain? 10.12.2015 (<https://tinyurl.com/u2bv4rz>); International Business Times, World's first ibuprofen patch developed delivering pain relief directly to the skin, 09.12.2015 (<https://tinyurl.com/43j5caj9>); Reuters, Ibuprofen patch heralds side effect free drug future, 22.02.2016 (<https://tinyurl.com/4z5ec35b>)

[5.5] Statement from CEO of Mercia Technologies

[5.6] Press release, Innovate UK awards Medherant a Medicines Manufacturing Grant, 03.10.2018 (<https://tinyurl.com/yf54fczh>) plus UK government industry strategy fund case study: Medherant: pioneering drug delivery through the skin, 05.03.2019 (<https://tinyurl.com/z6amfcdf>)

[5.7] Statement from Head of Operations and Programme Management at Cycle Pharmaceuticals, plus press release, Cycle Pharmaceuticals and Medherant Partner to Develop Medicines using the TEPI Patch® Technology, 05.05.2020 (<https://tinyurl.com/nat3ayhb>)