MedPharm

Breaking through boundaries

THE FOURTH INDUSTRIAL REVOLUTION – ROBOTICS AND THE LABORATORY

In this article, Marc Brown, PhD, Co-Founder and Chair of Scientific Committee, and Jon Lenn, PhD, Chief Scientific Officer, both at MedPharm, look at the company's implementation of automated robotic systems in enhancing workflow and the company's plans for the future implementation of robotics in formulation development.

Industry has been rapidly advancing since the 18th century with distinct periods of growth, or "revolutions", sparked by major innovations. The introduction of steam and electricity were the first two waves of the industrial revolution that radically changed the manufacturing economy on a global scale. The ability to harness power led to the rapid growth of technological innovations to automate previously manual tasks, resulting in more efficient production. The third industrial revolution was realised with the invention of computers, electronics and data storage. We are now in the middle of a fourth industrial revolution that seeks to combine physical and cyber technological advances. But how does this apply to life sciences and laboratory services, such as those offered by MedPharm?

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AUTOMATING SAMPLE PREPARATION

Any well-controlled experiment has the capacity to generate a large number of samples, and the sample volume can grow exponentially when laboratory experiments can run on a continuous cycle. Many laboratory tasks lend themselves to automation, thereby freeing experienced scientists to think critically, process data and provide complex interpretation, contextualisation and risk mitigation strategies for clients.

MedPharm's approach to integrating this fourth revolution was to critically evaluate the experimental workflow from end-to-end. Many experimental assays have been redesigned using a higher throughput approach. Simply switching sample collection to standard microplates allows for integration between microplates, instrumentation and equipment from different suppliers. MedPharm uses liquid-handling robots for routine sample preparation, which are further coupled with sample managers attached to analytical instrumentation. This allows samples to be processed and analysed 24 hours a day in parallel to other experiments. This automated workflow has been implemented in MedPharm's analytical, preformulation performance testing and tissue culture departments. This higher throughput approach has decreased timelines, cut down on experimental variation, tightened precision and decreased inaccuracies.

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AUTOMATION OF IVPT, IVRT, PREFORMULATION AND PROCESS DEVELOPMENT

In vitro release testing (IVRT) and *in vitro* permeation testing (IVPT) are two critical tests and the gold standard for the development of any topical or transdermal product. The systems or diffusion cells used in these experiments were developed decades ago – well before higher throughput experimental design was conceived. The original systems are highly manual, requiring scientists to spend a large amount of time to set up, collect and process the samples. Many commercially available systems do not consider sample collection standards, thereby limiting the integration into other instrumentation. MedPharm's approach was to develop and engineer its own systems based on the company's 25 years of experience with the older platforms. Some of the key concepts that were built into these designs were automation of the experiment, sample collection in microplates, optimised fluidics for human tissue (e.g. IVPT) and synthetic membranes (e.g. IVRT), and computer-controlled data collection.

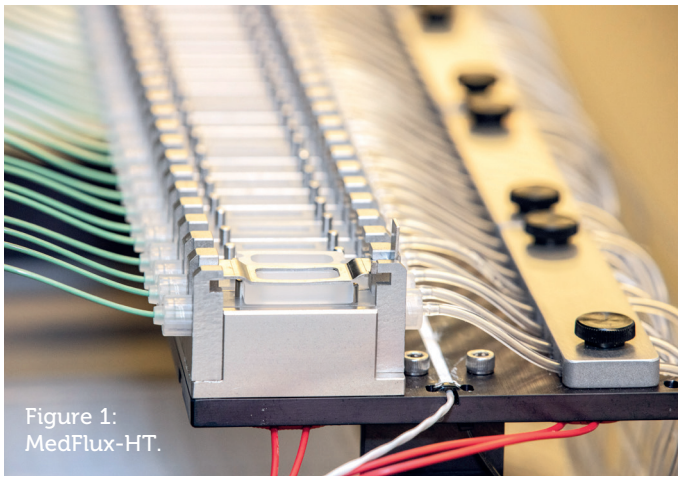

Figure 1: MedFlux-HT.

MedPharm's automated flow-through diffusion cells (MedFlux-HT®) are used routinely for IVPT experiments for R&D and regulated studies (Figure 1). This system has an integrated transepidermal water loss (TEWL) instrument that measures 32 diffusion cells simultaneously to ensure that the tissue maintains its barrier integrity. The TEWL instrument has an adapter that can be attached to Transwell permeable supports (Corning, NY, US) for experiments that use reconstructed tissue (e.g. skin, mucosal membranes, respiratory and eye).

MedPharm's automated vertical diffusion cell system (MedStat-HT®) is routinely used for IVRT where synthetic membranes are used in experiments to optimise thermodynamics, compare product sameness and as a quality control during product development (Figure 2). One example of design improvement is sample collection using highly precise and reproducible peristaltic pumps that self-eliminate air bubbles (a common problem in manual systems). This system also integrates computer-controlled sample collection and simultaneous receptor solution collection into microplates.

Figure 2: MedStat.

MedPharm has also implemented automated robotic systems such as the KingFisher™ Flex Purification System (Thermo Fisher Scientific, MA, US) in its tissue culture labs. This fully automated system yields high-speed purification of nucleic acids, proteins and cells using a similar microplate approach and has generated excellent reproducibility and quality.

Additionally, MedPharm has incorporated automation into preformulation and process development workflows. MedPharm's use of liquid handlers and robots to automate steps in preformulation allows drug solubility and stability to be assessed more accurately within various solvents and solvent systems, reducing the risk in variability when compared with human sampling. When assessing longer-term physical stability, automated instrumentation, such as a LUMiSizer® (LUM, Berlin, Germany), provides a more accurate prediction when compared with the harsher centrifugation technique, where marketed products are often observed to phase separate. Within process development and scale-up, MedPharm uses IKA Lab (Oxford, UK) reactors for identification and optimisation of critical processing parameters and the reproducible manufacturing of larger batches in future development.

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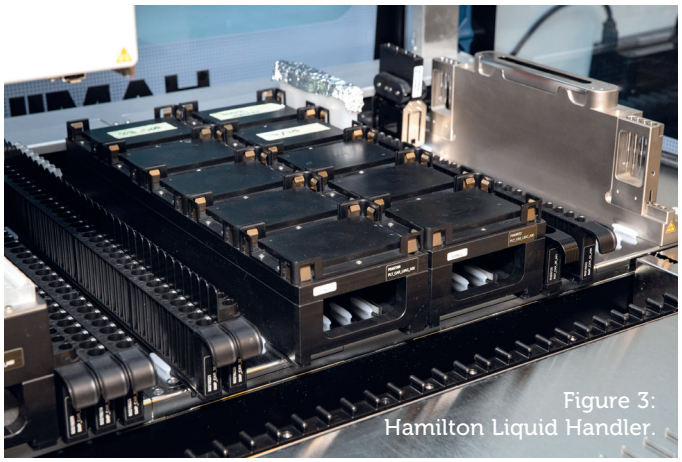

Figure 3: Hamilton Liquid Handler.

THE FUTURE

The next steps for MedPharm will be to implement robotics in formulation development. These robotics have similarities to liquid-handling robots, such as the Hamilton Liquid Handler (Figure 3), but are specifically designed to handle a range of excipients with complex viscosities used in the development of semi-solid formulations. These platforms integrate low powder weighing capability (low milligrams) to allow compound sparing when clients have a limited amount of active substance but will also allow for a much larger design of experiments to increase excipient testing.

MedPharm has over 25 years of experience in developing topical and transdermal products – meaning it has performed millions of experiments with the outcomes interpreted by the company's expert scientists. The next step is to develop structured databases or "large data" that can be mined for experimental trends relating to physiochemical properties, excipient compatibility, chemical solubility and stability, product performance, biological delivery and activity. This data could ultimately be used in machine learning (e.g. artificial neural networks) to identify trends that can be used in predictive experimental designs.

ABOUT THE COMPANY

MedPharm is a leading global contract provider of topical and transdermal product design and formulation development services. MedPharm are experts at reducing risk and accelerating development timelines for proprietary pharmaceutical and generic customers through their unique, cost-effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations. MedPharm is recognised for its scientific rigor by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK, with over 20 years of experience developing topical products.

ABOUT THE AUTHORS

Professor Marc Brown, PhD, is the Chair of Scientific Committee, co-founded MedPharm in August 1999 and has been the guiding force behind MedPharm's scientific developments and intellectual property. He has held the position of Professor of Pharmaceutics in the School of Pharmacy, University of Hertfordshire (UK) since 2006 and retains visiting/honorary professorships at the Universities of Reading (UK) and King's College London (UK). He has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of over 55 products that are now on the market in Europe, America and Japan. Prior to MedPharm, he was an academic in the Pharmacy Department at King's College London.

Dr Jon Lenn, Chief Scientific Officer, has direct responsibility for MedPharm's operations in the US based out of its facility in Durham, NC. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience in developing dermatological projects with Connetics, Stiefel and GSK and has been directly involved with the development and approval of eight products. He received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

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SMARTER TOPICAL AND TRANSDERMAL SOLUTIONS

FORMULATION DEVELOPMENT

PERFORMANCE TESTING

GMP MANUFACTURE

INDUSTRY & REGULATORY EXPERTISE

TRANSDERMAL PATCHES

LIQUID AND SEMI-SOLIDS

AEROSOL FOAMS AND PUMP SPRAYS

KNOWLEDGE WHERE YOU NEED IT

NEW CHEMICAL ENTITY/ RX
We guide clients from initial concept through to registration of a commercial product

OVER THE COUNTER
Our scientists can develop unique and propriety *in vitro* models as supporting evidence

GENERICS
We can support you in achieving generic approval using *in vitro* bioequivalence testing

SKIN **NAILS** **EYE** **AIRWAYS** **MUCOSAL MEMBRANES** **EAR**

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