Institution: University of Nottingham

Unit of Assessment: Chemistry UoA8

Title of case study: Supercritical Fluids – Critical Pharmaceuticals Ltd (**CS1**)

1. Summary of the impact

The University of Nottingham's School of Chemistry has developed a novel method of incorporating thermally or chemically labile biologically active substances into polymers. This has been achieved by using supercritical carbon dioxide as a medium for the synthesis and modification of polymeric materials. The method has been employed as the basis for new drug-delivery devices whose viability in the healthcare sphere has been confirmed by patient trials. The spin-out company, Critical Pharmaceuticals Ltd, has delivered a range of economic benefits, including job creation, the securing of millions of pounds' worth of investment and a number of revenue-generating research collaborations.

2. Underpinning research

The effective use of polymers in bio-materials has traditionally involved a number of significant challenges. In particular, maintaining the structure and activity of biological materials within polymers using conventional processing methods – for example, organic/aqueous solvent interfaces, elevated temperatures or the mechanical agitation of solutions – is difficult. In 1996, after a study of the literature (including the foaming and processing of polymers in tissue engineering) highlighted areas in which improvements in bio-materials processing were needed, the School of Chemistry at the University of Nottingham (UoN) began investigating the application of supercritical fluids for incorporating thermally or chemically labile biologically active substances into polymers.

Supercritical carbon dioxide ($scCO_2$) is known to be a "green" solvent with a broad range of environmentally sustainable chemistry applications. Working in collaboration with Vladimir Popov, of Moscow's Russian Academy of Sciences, Professor Steven Howdle (Professor of Chemistry, 1989-present) discovered that $scCO_2$ plasticises polymers and can be used not only to generate porous scaffolds but also to incorporate thermally labile molecules without loss of their activity. Examples included growth hormone yielding polymeric materials suitable for tissue engineering applications in the field of bone repair. This finding is the subject of a patent application [3.i] filed by UoN.

The researchers showed that the use of this supercritical fluid mixing method for producing a sustained release formulation had considerable advantage over existing commercial technologies as the drug is not chemically modified during the process. As a result there are no changes in activity, stability, safety and distribution of the active ingredients. Moreover, the process of encapsulation operates at ambient temperatures meaning that the technique could be applied to a range of thermally sensitive molecule such as proteins. The process is also solvent-free so there is no possibility of solvent residues contaminating the formulations and causing potentially harmful side-effects in patients.

The key finding that polymer-drug scaffolds could be formed using $scCO_2$ and without using any hazardous chemical solvents/reagents made the technology immediately amenable to biomedical applications. Howdle collaborated with UoN's School of Pharmacy (Professor Kevin Shakesheff, Professor of Advanced Drug Delivery and Tissue Engineering, 1997-present; Professor Martyn Davies, Professor of Biomedical Surface Chemistry, 1985-present) to explore these possibilities further and secured an EPSRC Materials Processing for Engineering Applications grant (MaPEA) [3.a] to investigate scale-up and commercialisation. This research included the optimisation of the supercritical mixing method and the testing of new polymer scaffolds for tissue engineering [3.1-3.3].

It was found that proteins could be mixed with plasticised polymers under $scCO_2$ conditions and the mixture sprayed to produce polymeric microparticles loaded with active protein. This could then be injected and would deliver the biologically active substance in a controlled release manner. Protein activity was also found to be unaffected by the supercritical mixing process [3.1]. A process was subsequently developed to allow encapsulation of delicate protein-based drugs or hormones into a biodegradable polymeric matrix, either as a scaffold for tissue engineering applications or as microparticles for controlled drug release.

The MaPEA research highlighted the commercial potential of using supercritical fluids as a reaction medium for the manufacture of polymer-based biomaterials. Dr Martin Whitaker, the PhD researcher on the grant, became a Business Science Fellow within the School's Business Partnership Unit and developed a business plan to establish a spin-out company, leading to the founding in 2002 of **Critical Pharmaceuticals Ltd**.
Research findings were published in 2002 & 2007 [3.2 & 3.3] and two further patents were filed by Critical Pharmaceuticals [3.ii & 3.iii].

3. References to the research (indicative maximum of six references)

Publications:

1. Howdle, S. M., Watson, M., Whitaker, M., Shakesheff, K. M., Davies, M. C., Mandel, F. S., Wang, J. D., and Popov, V. K, Supercritical fluid mixing: preparation of thermally sensitive polymer composites containing bioactive materials, *Chemical Communications*, 2001, 109-110, DOI: 10.1039/b008188o

2. Watson, M. S., Whitaker, M. J., Howdle, S. M., and Shakesheff, K. M., Incorporation of proteins into polymer materials by a novel supercritical fluid processing method, *Advanced Materials***,** 2002, **14**, 1802-1804, DOI: 10.1002/adma.200290003

3. Kanczler, J. M., Barry, J. J. A., Ginty, P., Howdle, S. M., Shakesheff, K. M., and Oreffo, R. O. C., Supercritical carbon dioxide generated vascular endothelial growth factor encapsulated poly(DL-lactic acid) scaffolds induce angiogenesis *in vitro*, *Biochemical and Biophysical Research Communications*, 2007, **352**, 135-141, DOI: 10.1016/j.bbrc.2006.10.187

Grants:

a. EPSRC Materials Processing for Engineering Applications Grant GR/M38759/01, Manufacturing of Bio-interactive Scaffolds for Tissue Engineering Using Supercritical Fluid Technology, P.I Steven M. Howdle, 1999-2001, £251,328

Patents:

i. Steven Melvyn Howdle Biofunctional polymers prepared in supercritical fluid WO9851347
ii. Andrew Naylor, Andrew Lester Lewis, Lisbeth Illum Process for preparing microparticles WO2010004287
iii. Lisbeth Illum, Michael Faron Jordan, Andrew Lester Lewis Improvements in the absorption of therapeutic agents across mucosal membranes or the skin WO2010029374

4. Details of the impact

UoN's novel method of using supercritical carbon dioxide as a medium for the synthesis and modification of polymeric materials has resulted in the development of new drug-delivery devices and millions of pounds' worth of investment and research collaborations for the spin-out company, Critical Pharmaceuticals Ltd (CP).

The method developed from the initial patent [3.i], marketed by CP as CriticalMix^{TM}, has been used to produce a human growth hormone (hGH), product CP016. In October 2008 this sustained release formulation of the synthetic hGH somatropin successfully completed preclinical studies in non-human primates, confirming that CriticalMix^{TM} enables sustained release of active species – as predicted – and that the therapeutic plasma levels are maintained for days, weeks or even

months following a single injection [5.1- 5.3].

Given the inherent shortcomings of the conventional hGH treatment regimen, these results are highly significant. hGH is used therapeutically to treat a variety of diseases – from growth hormone deficiency in children and adults to Turners Syndrome and HARS, a syndrome associated with HIV infection – but, due to various physical and biological barriers, it needs to be injected subcutaneously every day. The regimen is strongly disliked by patients and carers, with studies showing up to 66% of the former do not adhere to the prescribed routine, leading to reduced efficacy and increased healthcare costs. CP016 needs to be injected only once every two weeks, improving clinical outcomes through enhanced efficacy, greater patient compliance and reduced side-effects. A Non-Executive director of CP noted "despite the marked improvements in needle and injector pen technology, there remains a sizeable number of patients who have "needle phobia" and fail to adhere to the prescribed regimen" and that the technology "would be an important addition to the clinician's armamentarium" [5.4].

CP is also engaged in several new projects to increase the utility of CriticalMix™ including collaboration with UK biotechnology company PolyTherics Ltd. This partnership, launched in 2011 and backed by £350k of Technology Strategy Board funding [5.4], was initiated to produce a clinically superior sustained release product that could be administered less frequently than currently marketed products, resulting in reduced side-effects and improved overall efficacy. The Chief Executive Officer of PolyTherics has described the collaboration as "an opportunity to develop a unique technology... to produce a better product for patients" [5.5]. In addition in a collaboration with Ferring Pharmaceuticals which began in 2011, from pre-clinical results, CriticalMix™ technology has been shown to "overcome issues of release of Ferring's molecule which could not be overcome using standard drug delivery" [5.6]. Both of these examples demonstrate the significant impact CriticalMix™ has for patients.

Working with the UoN research team, CP has developed a second proprietary technology, CriticalSorb™, which allows hGH and other drugs to be administered using a nasal spray. CriticalSorb™ is a pharmaceutically acceptable excipient approved by the Food and Drug Administration as GRAS ("generally regarded as safe"). It has a Drug Master File and is used in currently marketed products as a solubility enhancer for intravenous and oral administration. It was found to be non-toxic in preclinical toxicology studies and was well tolerated by the nasal mucosa in acute, 14-day and six-month repeated dose chronic toxicity studies. It is not mutagenic to bacteria, mammalian cells and mammals, and no developmental toxicity or teratogenicity has been found. hGH could previously not be absorbed through the nasal mucosa, but CriticalSorb™ has been shown to allow it to be administered intra-nasally – thereby completely removing the need for daily injections.

CriticalSorb™ underpinned the development of the hGH treatment CP024, which in July 2012 successfully completed Phase I clinical trials in which it exhibited similar performance and safety to marketed products [5.7]. The trials also showed CP024 to be the first intra-nasal growth hormone to induce the insulin-like growth factor IGF-1. This represents a significant advance in efforts to treat the disorders related to hGH deficiency outlined above while obviating the need for injections. The growth hormone market is currently worth $3.1bn, with more than 10 major manufacturers of branded and generic daily injectable products. CP024 is the only non-invasive growth hormone product in development, and feedback from leading endocrinologists and franchise holders indicates it is an attractive product for patients and physicians.

CriticalSorb™ has also been used in two revenue-generating research collaborations with biotechnology companies and in a major collaborative project with Nottingham's Queen's Medical Centre, the largest hospital in the UK and Europe's largest teaching hospital, to evaluate a new nasal delivery formulation for Teriparatide, a treatment for osteoporosis [5.8]. This new formulation is expected to improve the efficacy of the drug and make it more easily administered as it eliminates the current need for daily subcutaneous injection. To date the collaboration has demonstrated excellent outcomes in preclinical studies and will start Phase I clinical trials in October 2013. The Head of The Clinical Gerontology Research Unit at Nottingham University

Hospitals NHS Trust [5.9] expects the nasal teriparatide product to 'significantly benefit patients, their families, carers and clinicians with improved clinical outcomes and greatly enhanced ease of use' and 'enable patients to live independently for longer so reducing the cost of treatment'.
The progress made in exploiting these technologies is in line with the drug discovery and development timeline expected when bringing a new drug/therapy to market – specifically, up to 15 years from inception.

UoN's research has enabled CP to safeguard nine jobs and has also allowed expansion, with a further six staff recruited since 2008. In the period 2008-2013, CP has attracted £2.7m in private investment and venture capital and another £1.9m in R&D funding, including £1.5m from the Wellcome Trust (October 2009) [5.10] to develop CriticalSorb^{TM}. Investors have described CP as "an exciting opportunity" and "an ideal showcase for the region's excellence in pharmaceutical services" [5.11]. A number of revenue-generating research collaborations have been secured using the CriticalMix^{TM} technology, including with a leading European pharmaceutical company, seven biopharmaceutical companies and two drug-delivery companies.

5. Sources to corroborate the impact

1. Preclinical results of CriticalMix^{TM} hGH product http://www.criticalpharmaceuticals.com/latest/news/critical-pharmaceuticals-enter-sustained-release-hgh-arena (published 1/10/08, accessed 25/9/12)

2. Jordan, F., Naylor, A., Kelly, C., Howdle, S., Lewis, A., and Illum, L., Sustained release hGH microsphere formulation produced by a novel supercritical fluid technology: *in vivo* studies, *Journal of Controlled Release*, 2010, **141**, 153-160, DOI: 10.1016/j.jconrel.2009.09.013

3. Kelly C., Naylor A., Illum L., Shakesheff K. M., and Howdle S., Supercritical CO_2: A Clean and Low Temperature Approach to Blending $P_{DL}LA$ and PEG, *Advanced Functional Materials*, 2012, **22**,1684-1691, DOI: 10.1002/adfm.201101889

4. Letter of support from Non-Executive director of Critical Pharmaceuticals (11/10/13)

5. Critical Pharmaceuticals/PolyTherics Ltd TSB-funded collaboration http://www.criticalpharmaceuticals.com/latest/news/polytherics-and-critical-pharmaceuticals-collaboration (published 5/4/11, accessed 25/9/12)

6. Senior Vice President Global Pharmaceutical R&D Ferring Pharmaceuticals (14/10/13)

7. CP024 Phase I clinical trial outcomes http://www.criticalpharmaceuticals.com/latest/news/cp024-presentation-at-endo (published 7/6/12, accessed 25/9/12)

8. TSB and EPSRC funding to develop nano-enabled nasal spray for osteoporosis http://www.criticalpharmaceuticals.com/latest/news/nasal-pth-collaboration (published 16/2/12, accessed 25/9/12)

9. Letter of support from the Head of The Clinical Gerontology Research Unit at Nottingham University Hospitals NHS Trust (18/9/2013)

10. Wellcome Trust funding http://www.criticalpharmaceuticals.com/latest/news/wellcome-trust-funding-for-cp024-nasal-hgh (published 14/10/09, accessed 25/9/12)

11. Investment round results http://www.criticalpharmaceuticals.com/latest/news/critical-pharmaceuticals-raise-650k (published 10/11/08, accessed 25/9/12)