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| **Institution:** University of Bradford | | |
| **Unit of Assessment:** B12 Engineering | | |
| **Title of case study:** A new thermoplastic granulation process for nutraceutical manufacture reduces production costs, improves quality and increases business resilience. | | |
| **Period when the underpinning research was undertaken:** 2001 - 2020 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** | **Role(s) (e.g. job title):** | **Period(s) employed by HEI:** |
| Prof Adrian Kelly | Professor of Process Engineering | 1997 – present |
| Prof Tim Gough | Professor of Fluid Mechanics | 2000 – present |
| Prof Anant Paradkar | Professor of Pharmaceutical Eng. | 2008 – present |
| Prof Phil Coates | Professor of Polymer Engineering | 1978 – present |
| Dr Mohammad Isreb | Lecturer in Pharmaceutics | 2011 – present |
| **Period when the claimed impact occurred:** 2016-2020 | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

## 1. Summary of the impact (indicative maximum 100 words)

Cross disciplinary pharmaceutical engineering has been a focus of research at the University of Bradford since 2008. In 2015, a KTP with Health Innovations Ltd (HI) led to the successful deployment of thermoplastic granulation (TPG) to manufacture nutritional supplements. As a result, over 45 TPG-based products have been launched in the UK and European markets. Since embedding TPG technology in their products, HI has made over GBP400,000 of cost savings, created 8 new jobs and saved 11, whilst investing more than GBP3,000,000 that enhanced its capabilities, capacity, and revenues.

## 2. Underpinning research (indicative maximum 500 words)

The Centre for Pharmaceutical Engineering Science (CPES) was founded in 2010 following collaboration between academics in the fields of polymer engineering and pharmaceutical science. The Polymer Interdisciplinary Research Centre at Bradford has a long track record of research delivery related to materials processing and characterisation as evidenced by [1] and (GR1). CPES was formed in response to a growing interest in the application of polymeric materials to deliver active pharmaceutical ingredients, having received pump-prime funding from the University to develop its experimental capabilities within this novel field. Profs Kelly, Gough and Paradkar initially developed amorphous solid dispersions [3] and cocrystals [2] using continuous solvent-free processes [4]. CPES has since expanded and successfully led a number of research projects, PhDs and KTPs in the broad area of solvent-free processing of pharmaceutical materials, with particular emphasis on the control of drug release. The team has explored the application of shear-assisted melt processing of nutraceutical and pharmaceutical molecules, including amorphisation (GR5), new crystal phases and simultaneous agglomeration. Fundamental research has been supported by EPSRC funded projects: A Novel Continuous Method for Co-crystal Formation (GR2) and Global Partnerships (GR3). The main outcome of this research has been improvements in the understanding of phase transformation and agglomeration of particles in a solvent-free environment, under moderate to high-shear fields. This has led to the development of the TPG process and its application to develop temperature and moisture sensitive nutritional supplements through a KTP (GR6). TPG involves agglomeration of powdered material using a melt binder instead of solution-based binders and has major advantages including: solvent-free processing and avoiding time and energy consumed downstream in the wet-granulation drying step.

The fundamental underpinning research has included: a) understanding thermal and rheological performance of the polymer melt under different shear regimes; b) the relationship between surface properties of the powder and melt binder [6], and c) mechanistic understanding of TPG process, including changes in shape and internal structure of the granules with shear and time. This has been complemented by industrial research, such as the development of a feasibility model based on a Material Properties and Product Performance (MPPP) database, for the development of a TPG process for different formulations. TPG scale-up has been achieved using a bottom blade high-shear granulator (1000L capacity), with a regulatory approved melt binder.

Health Innovation Ltd, an SME in the Yorkshire region, collaborated with CPES to develop an in-house TPG process for its nutritional supplements. The Company previously imported pre-granulated materials, which presented processing issues. Furthermore, importing materials involved significant transport time, cost, and in-turn a high carbon footprint. The initial feasibility study (supported by the ERDF funded Yorkshire Innovation Fund) addressed these issues and was followed by a KTP between HI and CPES [5]. The KTP project involved investigations into the material properties, regulations, and processes connected to the Company's supplements. A model was developed, using Material Property Product Performance (MPPP) database, to predict the quality of granules produced, and to optimise the melt binder and processing parameters to formulate each material. The technology was successfully transferred to HI and scaled-up to a commercial batch size of 400kg.

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

1) Kelly, AL, Brown, EC and Coates, PD (2006) The Effect of Screw Geometry on Melt Temperature Profile in Single Screw Extrusion, Polymer Engineering and Science, 46 (12): 1706-1714. https://doi.org/10.1002/pen.20657

2) Paradkar, A, Dhumal, RS, Kelly, AL, York, P, Coates, PD (2010) Cocrystalization and simultaneous agglomeration using hot melt extrusion. Pharmaceutical Research, 27 (12): 2725-2733. https://doi.org/10.1007/s11095-010-0273-9

3) Kulkarni, CS, Kelly, AL, Kendrick, J, Gough, T and Paradkar, AR (2013) Mechanism for polymorphic transformation of artemisinin during high temperature extrusion. Crystal Growth and Design, 13: 5157-5161. https://doi.org/10.1080/03639045.2017.1386200

4) Korde, S, Pagire, S, Pan, H, Seaton, C, Kelly, A, Chen, Y, Wang, Q, Coates, P, Paradkar, A (2018) Continuous Manufacturing of Cocrystals Using Solid State Shear Milling Technology. Crystal Growth and Design, 18 (4): 2297-2304. https://doi.org/10.1021/acs.cgd.7b01733

5) Aher, S; (2018) Knowledge Transfer Partnership Associate, Final Report

6) Kitching, VR, Rahmanian, N, Jamaluddin NH, Kelly, A. (2020) Influence of Type of Granulators on Formation of Seeded Granules. Chemical Engineering Research and Design, 160: 154-161. https://doi.org/10.1016/j.cherd.2020.05.017

**Grants**

GR1) Kelly (PI) In-process Metrology for the UK Polymer Industry, DTI CHBJ/005/00110C, GBP225,000, 09/2006 – 08/2008

GR2) Paradkar (PI) A Novel Continuous Method for Co-crystal Formation, EPSRC EP/J003360/1, GBP495,364, 03-2012 – 07-2015

GR3) Coates (PI) GLOBAL - Promoting research partnerships in Advanced Materials for Healthcare, EPSRC EP/K004204/1, GBP499,989, 04-2012 – 03-2013

GR4) Paradkar (PI) Strategic intervention: Green Processing Technologies, ERDF YIF/SI/01, GBP251,044, 06-2013 – 06-2015

GR5) Kelly (PI) Hot Melt Extrusion Process Development, Innovate UK KTP009991 (AstraZeneca plc), GBP103,000, 09-2015 – 03-2017

GR6) Paradkar (PI) Solvent free, Thermoplastic Granulation Technology, Innovate UK KTP009978 (Health Innovation Ltd), GBP115,545, 11-2015 – 11-2017

GR7) Paradkar (PI) Innovation in Effervescent Product Manufacturing and Packaging, Innovate UK Smart Award 46718, GBP246,173, 07-2020 – 12-2021

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

Health Innovations Ltd (HI) is a manufacturer of vitamins, minerals and nutritional supplements who supply UK and international markets. In 2015, HI identified poor competitiveness in certain solid dosage products and identified a need to change its manufacturing procedures to enable business growth. Results from research into TPG at CPES and HI encouraged the Company to invest in a high-shear granulator (HSG) to granulate their own raw materials for tabletting (A).

**4.1. Commercial Impact**

4.1.1. A reduction in the cost of manufacture

TPG technology has led to a reduction in the cost of manufacture of tablets. Prior to adoption, HI purchased ready granulated raw materials from a German supplier at a premium cost. The company now purchase powder form raw materials from UK suppliers and manufacture these granules in-house, at a 20% saving. To date, over 160 tonnes of material have been granulated in-house using TPG technology and used in more than 45 products sold world-wide. This also allowed the company to change product composition, which has significantly reduced the unit cost of production. For example, material cost per unit of one high-volume multivitamin product dropped from GBP3.86 to GBP2.96 due to the use of “in-house” TPG processed material. Since implementation of the technology the company has made over GBP350,000 in material cost savings. Materials granulated in the company’s new facilities have better manufacturing properties than “bought-in” materials. These granulated materials are easier to tablet, significantly decreasing tabletting force, lowering the wear and tear on tablet punches/presses, and therefore leading to reduced maintenance costs (A, B).

4.1.2. Enhanced flexibility and protection of the supply chain for raw materials

TPG technology was adopted for 36 raw materials, giving far greater flexibility on sourcing, and allowing better purchasing power. Being previously tied to a limited number of suppliers, the Company now has a greater choice of materials and suppliers, so can push for lower prices with reduced risk. For example, during the recent Covid-19 lockdown, the cost of pre-granulated calcium carbonate from China rose from GBP0.90 to GBP8.50/kg and lead-times of 4 to 24 weeks. In-house granulation allowed HI to maintain an uninterrupted supply of products and maintain a competitive edge (A, B).

4.1.3. Improvements to the consistency of quality of final tablet products

Variations in the quality of pre-granular material, evident from previous suppliers, is no longer an issue and overall HI has greater control of its final products, with fewer rejected batches providing additional cost savings (A).

4.1.4. An increased manufacturing capacity leading to additional cost savings

The HSG facility can also mix powder blends for tableting. Powder mixing represents a bottleneck for nutraceutical tablet manufacturers. HSG can mix double the volume of mixes in 30% less time compared to standard blenders, allowing approximately 20% increased capacity and flexibility in mixing operations, thereby reducing weekend and night shift requirements. Annual savings of over GBP50,000 on staff were expected in 2020. For example, increased blending capacity and competitiveness has meant HI has purchased 2 new tablet machines, saving the business approximately GBP400,000 in 2020; it now produces over 180 million tablets/year, worth GBP2,700,000 in revenue (A).

4.1.5. Protection for the Company from post-Brexit uncertainties

HI is no longer dependent on supply of pre-granulated materials from the EU and is therefore protected from potential large increases in cost of goods due to Brexit. The local supply chain has benefits for UK plc and represents a positive environmental impact through reducing the carbon footprint of transport (A).

**4.2. Jobs generation**

The Company has saved 5 jobs at operator level by avoiding a reduction in business. HI has also created 8 new jobs, including the KTP Associate who was appointed process innovation manager, one formulation scientist (PhD), one manufacturing technician and five operators. The Company has strategically decided to develop innovative products based on TPG technology. The new roles of process innovation manager and formulation scientists were created to achieve this objective. The enhanced business capacity has created or saved at least 6 jobs in the supply chain, including packaging, transport, accounts, and finance (A).

**4.3. A change in innovation culture**

Through the TPG technology and HSG facility, HI has created new opportunities for innovation and collaboration and is currently working with CPES and an innovation start-up (Octopoda) using HSG for the large-scale manufacture of co-crystals. This project received an Innovate UK Smart Grant (GBP240,000 (D) and will strengthen the innovation culture in the company (C). HI and UoB were nominated as one of the top 3 finalists in the Business Impact category of 'The Best of The Best KTP Awards 2019'(D). As an indicator of the change in innovation culture, HI was shortlisted by Innovate UK and Enterprise Europe Network as an innovation led company for the 'Scale-up programme'. The Company will receive intensive support to achieve 50-100% growth/year.

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

A. Letter from Health Innovations CEO This details the cost savings, increased revenue, job creation and other benefits resulting from the collaboration with CPES.

B. KTP Final Report: KTP Associate Final Report, 2018
See sections 4 (Main project activities & outcomes) and 6 (Project effectiveness).

C. Letter from Octopoda Director
Detailing how the collaboration between HI and CPES has benefitted a new R&D company.

D. Novel Continuous Method for Co-crystal Formation
Evidence of impact resulting from a related CPES project in healthcare materials engineering.

D. Website links:
KTP Best of the best finalists! An announcement from Health Innovations on being selected as a finalist in the Innovate UK's Knowledge Transfer Partnership (KTP) Best of the Best 2019 awards (April 2019).

KTP Best of the Best Awards: a review (May 2019).
Description of award nominations resulting from the collaboration.