Institution: University of Bradford

Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Deployment of new thermoplastic granulation technology for the manufacture of nutritional supplements improves product quality, reduces production costs and creates skilled jobs in northern England

Period when the underpinning research was undertaken: 2008 - 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:
Prof A Paradkar	Professor of Pharmaceutical Engineering	2008 – present
Prof Phil Coates	Professor of Polymer Engineering	1986– present
Prof Adrian Kelly	Professor of Process Engineering	1997– present
Prof Tim Gough	Professor of Fluid Mechanics	2000– 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? N

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

Research into solvent-free shear-based technologies started at the University of Bradford in 2008, leading to a KTP with Health Innovations Ltd in 2015 and subsequently to the deployment of the process for thermoplastic granulation to manufacture nutritional supplements. Over 38 TPG based products were launched in the UK and European markets from June 2018. Since embedding of TPG technology HI have saved over GBP400,000, created 8 new jobs, saved 11 and invested over GBP3,000,000 to enhance its capabilities, capacity, and revenues. Based on impact, the Partnership was a finalist for the Best of the Best KTP Award 2019.

2. Underpinning research (indicative maximum 500 words)

Since 2008, academics at the Centre for Pharmaceutical Engineering Science (CPES) have actively studied solvent-free shear-based processing technologies. Professors Paradkar, Coates, Kelly, and Gough and Dr. Isreb have undertaken research across the full breadth of shear-based processes. This fundamental research, along with collaborative industrial research, including a Knowledge Transfer Partnership, led to the development of a thermoplastic granulation (TPG) process for temperature and moisture sensitive nutritional supplements. TPG involves agglomeration of powder material using a melt binder instead of solution-based binders and has major advantages over wet-granulation including solvent-free processing and avoiding time and energy consuming downstream drying step. Currently the mechanistic understanding of TPG is very limited due to the small number of materials explored as melt binders, and approved by regulatory agencies, in the nutritional supplement and pharmaceutical sector.

Fundamental research a. understanding thermal and rheological performance of the polymer melt under different shear regimes (1); b. the relationship between surface properties of the powder and melt binder and c. mechanistic understanding of TPG process, including changes in shape and internal structure of the granules, with shear and time (2).

Industrial Research a. development of a feasibility model based on a Material Properties and Product Performance database for the development of a TPG process for different formulations (3) b. TPG scale-up using a high-shear granulator (1000L capacity) and a regulatory approved melt binder.

Through collaboration between CPES and the Interdisciplinary Research Centre in Polymer Engineering (IRC) the research team has a strong track record in solvent-free shear-based processing of polymers and plastics. The team explored the application of shear-assisted melt processing of nutraceutical and pharmaceutical molecules, including amorphisation, new crystal phases and simultaneous agglomeration (5,6). The fundamental research was supported by the EPSRC funded projects: A Novel Continuous Method for Co-crystal Formation (EP/J003360/1), Science Bridges China (EP/G042365/1) and Global Partnership (EP/K004204/1). The main outcome was an understanding of phase transformation and agglomeration of particles in a solvent-free environment, under a moderate to high-shear environment (4) leading to the development of the TPG process and its mechanistic understanding for nutritional supplements (2).

Health Innovations Ltd (HI), an SME based in West Yorkshire, worked with CPES to develop an in-house TPG process for their nutritional supplements. The company previously imported pre-granulated materials which was problematic due lack of flexibility and a need for high compression force as the granules were produced dry. Furthermore, importing materials involved significant transport time, cost, and in-turn high carbon footprint. The initial feasibility study (supported by Yorkshire Innovation Fund) addressed these issues and was followed by a KTP between HI and CPES (KTP No.:KTP009978). The KTP project involved investigations into the material properties, regulations, and processes connected to the Company's supplements (3). A model was developed, using a Material Property Product Performance (MPPP) database, to predict the quality of granules produced and optimise the melt binder and processing parameters to formulate each material. The project investigated the changes, risks and costs required to convert to in-house granulation. The technology was successfully transferred to HI and scaled-up to commercial batch size of 400kg.

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

1. Paradkar, A. et al. (2010) Cocrystalization and simultaneous agglomeration using hot melt extrusion. *Pharmaceutical Research*, 27 (12): 2725-2733 https://doi.org/10.1007/s11095-010-0273-9

2. Korde, S., et al. (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

3. Aher, S. (2018) Knowledge Transfer Partnership Associate, Final Report.

4. Kulkarni, C.S., et al. (2013). Mechanism for polymorphic transformation of artemisinin during high temperature extrusion. *Crystal Growth and Design,* (13): 5157-5161 https://doi.org/10.1021/cg400891b

5. Wood, C., et al. (2016). Near infra-red spectroscopy as a multivariate process analytical tool for predicting pharmaceutical co-crystal concentration. *Journal of Pharmaceutical and Biomedical Analysis* (129): 172-181 https://doi.org/10.1016/j.jpba.2016.06.010

6. Kitching, V.R., et al. (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

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

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

Paradkar A, Solvent free, Thermoplastic Granulation Technology (KTP009978) Innovate UK, 11/2015 – 10/2017, GBP115,545

Paradkar A, Strategic intervention: Green Processing Technologies, (YIF/SI/01) Yorkshire Innovation Fund, 06/2013 – 06/2015, GBP251,044

Paradkar A, HI Smart Award: Innovation in Effervescent Product Manufacturing and Packaging, (KTP009991) Innovate UK (Project no 46718) 07/2021 –12/2021, GBP246,173

Kelly A, Hot Melt Extrusion Process Development, (KTP009991) Innovate UK, 09/2015 -03/2019 GBP103,000.

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

Health Innovations Ltd is a manufacturer of vitamins, minerals, and nutritional supplements, distributed in the UK, EU, and Middle East markets. In 2015, HI identified poor competitiveness in certain solid dosage products and a need to change its manufacturing procedures to enable business growth. Results from research into TPG at CPES and HI allowed the company in 2017 to invest in a high-shear granulator (HSG) to granulate their own raw materials for tabletting (A).

1. Commercial Impact

1.1 A reduction of the cost of manufacture

TPG technology led to a reduction in the cost of manufacture of tablets. Prior to adopting TPG technology, HI purchased ready granulated raw materials from a German supplier at a premium cost. The company now buy-in powder form raw materials from UK suppliers and manufacture these granules in-house at a 20% saving. To date, over 160 tonnes of material was granulated in-house using TPG technology and used in more than 45 products sold across the world. This allowed a change in product composition which reduced the unit cost significantly. For example, material cost per unit of one high-volume multivitamin product dropped from GBP3.86 to GBP2.96. Since implementation of the technology in 2018, the company has made over GBP350,000 in material cost savings. Materials granulated in their new facilities have better manufacturing properties than “bought-in” materials so easier to tablet, significantly decreasing tabletting force, lowering the wear and tear on tablet punches/presses, leading to reduced maintenance costs (A,B).

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, allowing better purchasing power. Being previously tied to a limited number of suppliers, the company now have a greater choice of materials and suppliers, so can push for lower prices with reduced risk. For example, during the recent Covid-19 lock-down, the cost of pre-granulated calcium carbonate from China went from £0.90 to £8.50/kg and lead-times 4 to 24 weeks. In-house granulation allowed HI to maintain uninterrupted supply of products and maintain a competitive edge (A,B).

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 meaning HI has greater control of final product quality; fewer rejected batches providing additional cost savings (A).

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 c.20% increased capacity, flexibility in mixing operations reducing weekend and night shift requirements. Annual savings of over GBP50,000 on staff was expected in 2020. For example, increased blending capacity and competitiveness has meant HI has purchased 2 new tablet machines, saving the business c.GBP400,000 in 2020; they now produce over 180 million tablets/year worth GBP2,700,000 in revenue (A).

1.5 Protection for the company from post-Brexit uncertainties

HI is no longer dependent on supply of pre-granulated materials from the EU so are protected from increases in cost of goods due to Brexit. The local supply chain has benefit to UK plc and represents a positive environmental impact (A).

2. Creation and retention of skilled jobs

The company has saved 5 jobs at operator level by avoiding loss of business. HI created 8 new jobs, including the KTP Associate appointed process innovation manager, one formulation scientist (PhD), one manufacturing technician and five operators. The company has 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).

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 innovation start-up Octopoda using HSG for large-scale manufacture of co-crystals. This project received an Innovate UK Smart Grant of GBP240,000 (D) and will strengthen the innovation culture in the company (F). HI and UoB were nominated top 3 finalists for 'The Best of The Best KTP Awards 2019' in the Business Impact Category (C). Indicative of the change in culture HI was shortlisted by Innovate UK and Enterprise Europe Network as an innovation led company for the Scaleup Programme. The company will receive support to achieve at least 50-100% growth/year.

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

A. Testimonial Letter from CEO Health Innovations Ltd

B. KTP Final Report: Aher, S. (2018) Knowledge Transfer Partnership Associate Final Report

C. 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.

KTP Best of the Best Awards: a review A review and reflection on the Awards. KTP Associate Dr Suyog Aher mentioned.

D. Smart Award (2020): A Novel Continuous Method for Co-crystal Formation

E. Individual users/beneficiaries who could be contacted by the REF team to corroborate claims.

- Process Innovation Manager at Health Innovations Ltd
- CEO of Health Innovations Ltd
- CFO of Health Innovations Ltd
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F. Letter from CEO Octopoda Ltd