Institution: University of Sunderland

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Faster, more efficient production of spray-dried drug-polymer solid dispersions

Period when the underpinning research was undertaken: 2005-date

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:**
Kalliopi Dodou	Associate Professor	2000-present

Period when the claimed impact occurred: 2018-December 2020

Is this case study continued from a case study submitted in 2014? N

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

Research led by Dodou has changed how a global pharmaceutical company develops spray-dried drug-polymer solid dispersions (SDSDs). The research set out to improve the screening processes used to develop formulations of new chemical entities, resulting in a **cost- and material-efficient screening protocol** used for screening SDSDs. This protocol improves on existing approaches by integrating processing properties which are traditionally tested after screening, thereby providing a **more accurate and efficient pathway from screening to manufacturing phases**. This new protocol has now been adopted commercially by UCB Pharma for the screening of all SDSDs and has enabled the company to bring screening work in-house, saving at least EUR 100,000 since 2018.

2. Underpinning research (indicative maximum 500 words)

Drug crystallisation in dosage forms is a **formulation defect** because it hinders drug release. Drug-in-adhesive films contain the drug in the adhesive thin layer that attaches the patch on the skin surface. Crystallisation of drugs in the adhesive layer is usually detected during QC stability testing before the patches are released to the market. However this is a challenging issue for the transdermal industry, which has led to the recall of some commercial patches such as Neupro. Since 2005 Dodou has conducted research to address this matter, focussing on the crystallisation of drugs in drug-in-adhesive transdermal films.

The stabilisation approach Dodou investigated was via the formation of amorphous drug-polymer solid dispersions (ASDs). The first milestone of the research on this topic was **the discovery that the manufacturing method of drug-polymer solid dispersions can affect both the crystallisation tendency of the drug in the adhesive layer and the solubility of the drug in the adhesive [R1].** In this work Ibuprofen was used as a model drug and poloxamer 188 as the polymeric carrier in different drug/polymer ratios. It showed that solid dispersions formulated via melting of the drug/polymer mixture in the adhesive layer provide crystal-free films of high drug loading capacity, and that the ratio adjacent to the eutectic composition exhibits the highest thermodynamic activity.

The research formed the basis of her **first collaboration with UCB Pharma**, a multinational biopharmaceutical giant headquartered in Belgium. Dodou was PI on this collaboration, working with scientists in the company's drug delivery design and development team. The collaboration achieved a second milestone; the **development of novel thermodynamic predictive models** that enable the estimation of the required polymer amount to stabilise, over long-term storage conditions, a given drug concentration in the adhesive layer of transdermal patches **[R2]**. This work was fully funded by UCB Pharma.

The findings highlighted the use of theoretical thermodynamic models in the prediction of the long-term stability of drug/polymer amorphous solid dispersions and led to Dodou's **second collaboration with UCB Pharma** on the systematic investigation of the theoretical prediction of

drug-polymer miscibility and how the determination of drug-polymer miscibility at small manufacturing scale could correlate with the large-scale manufacture of solid dispersions. This work was fully funded by UCB Pharma.

Having thus established that the **theoretical thermodynamic models cannot accurately predict drug/polymer miscibility [R3],** they addressed the issue by **developing a novel effective miniaturised screening device** for the prediction of drug-polymer miscibility at an industrial pre-formulation stage **[R4]**, and a **novel small-scale spray-drying approach** for the miscibility of drug/polymer solid dispersions at early drug development **[R5]**.

These findings culminated in the derivation of **a novel industrial protocol [R6]** which is the focus of this impact case study. The protocol improves on existing approaches by integrating processing properties which are traditionally tested after screening. In this way, the protocol is a more accurate and direct pathway from screening to manufacturing phases.

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

R1 Dodou, Kalliopi and Saddique, Waqaas (2012) *Effect of manufacturing method on the in-vitro drug release and adhesive performance of drug-in-adhesive films containing binary mixtures of ibuprofen with poloxamer 188.* Pharmaceutical Development and Technology, 17 (5). pp. 552-561. ISSN 1083-7450

R2 Chenevas-Paule, Clemence, Wolff, Hans, Ashton, Mark, Schubert, Martin and Dodou, Kalliopi (2017) *"Development of a predictive model for the long term stability assessment of drug-in-adhesive transdermal films using polar pressure sensitive adhesives as carrier/matrix.".* Journal of Pharmaceutical Sciences, 106 (5). pp. 1293-1301. ISSN 0022-3549

R3 Ousset, Aymeric, Chavez, Pierre-François, Meeus, Joke, Robin, Florent, Schubert, Martin Alexander, Somville, Pascal and Dodou, Kalliopi (2018a) *Prediction of Phase Behavior of Spray-Dried Amorphous Solid Dispersions: Assessment of Thermodynamic Models, Standard Screening Methods and a Novel Atomization Screening Device with Regard to Prediction Accuracy.* Pharmaceutics, 10 (1). pp. 29-54. ISSN 1999-4923

R4 Ousset, Aymeric, Meeus, Joke, Robin, Florent, Schubert, Martin, Somville, Pascal and Dodou, Kalliopi (2018b) *Comparison of a Novel Miniaturized Screening Device with Büchi B290 Mini Spray-Dryer for the Development of Spray-Dried Solid Dispersions (SDSDs).* Processes, 6 (8). p. 129. ISSN 2227-9717

R5 Ousset, Aymeric, Bassand, Celine, Chavez, Pierre-Francois, Meeus, Joke, Robin, Florent, Schubert, Martin Alexander, Somville, Pascal and Dodou, Kalliopi (2018c) *Development of a small-scale spray-drying approach for amorphous solid dispersions (ASDs) screening in early drug development.* Pharmaceutical Development and Technology.

R6 Ousset, Aymeric, Chirico, Rosanna, Robin, Florent, Schubert, Martin, Somville, Pascal and Dodou, Kalliopi (2018d) *A Novel Protocol Using Small-Scale Spray-Drying for the Efficient Screening of Solid Dispersions in Early Drug Development and Formulation, as a Straight Pathway from Screening to Manufacturing Stages.* Pharmaceuticals, 11 (3). p. 81. ISSN 1424-8247

Evidence of quality of research

The research externally funded:

- Transdermal patches. UCB Pharma. PI: Dodou. 2013-16. £40,113
- Drug polymer solid dispersions. UCB Pharma. PI: Dodou. 2014-19. £91,793.

Journal rankings:

- **R1, R2 and R6** are published in Q1-ranked Pharmaceutical Science journals**.**
- **R3, R4 and R5** are published in Q2-ranked Pharmaceutical Science/Process Chemistry and Technology journals.

R6 provides a conclusive solution to a problem faced by all pharmaceutical developers producing SDSDs. The body of research is highly relevant and of significance to any pharmaceutical developer producing SDSDs and has proven application in pharmaceutical development.

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

Since 2005 Dodou has worked in partnership with the drug delivery design and development group at UCB Pharma. Spray dried solid dispersion (SDSD) products are a key part of the UCB new chemical entities pipeline for both non-clinical and clinical development. The significance of this pipeline prompted UCB to appoint an expert partner to provide new insights into manufacturing methodologies and quality control tools for the development of poorly water-soluble drugs, with the aim of developing a more accurate protocol for quality control that would be used to optimise drug stability and speed up the drug development process.

Dodou's research demonstrated that standard screening tools used in development of spray-dried solid dispersions (SDSDs) do not fully account for the effect of the preparation method on the properties of screened ASDs **[R6]**. This inaccuracy meant that additional experimentation is needed, resulting in a more time-consuming and wasteful process with additional costs. Dodou's protocol is more accurate because it incorporates the processing method throughout development of the active pharmaceutical ingredient (API), therefore removing the need for additional experimentation, creating a faster, less wasteful (and therefore cheaper) screening process. UCB implemented the new protocol in August 2018 for the screening of all SDSDs in their pipeline in both clinical and non-clinical development.

By removing the need for further post-screening experimentation, **the protocol has reduced API consumption from 10g to 735mg, and screening/formulation time from 16 weeks to 9 days [R6].** Prior to this research UCB outsourced their solid dispersion screening at a cost of approximately EUR 10,000 – 15,000 per molecule; each year approximately 5 molecules are selected as potential solid dispersion candidates. This screening tool has removed the need for outsourcing this activity, thus saving between EUR 50-75,000 per year, or EUR 100-150,000 during the assessment period. The change has also enhanced the organisation's capacity for development of new molecules: "*Adoption of this new time- and material-efficient protocol has made an impact on UCB Pharma's capacity to speed up the lead discovery and lead optimization phases up to the clinical development of pipelines' molecules*" **[S1].**

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

S1 Written testimonial from Drug Product Lead, UCB Pharma