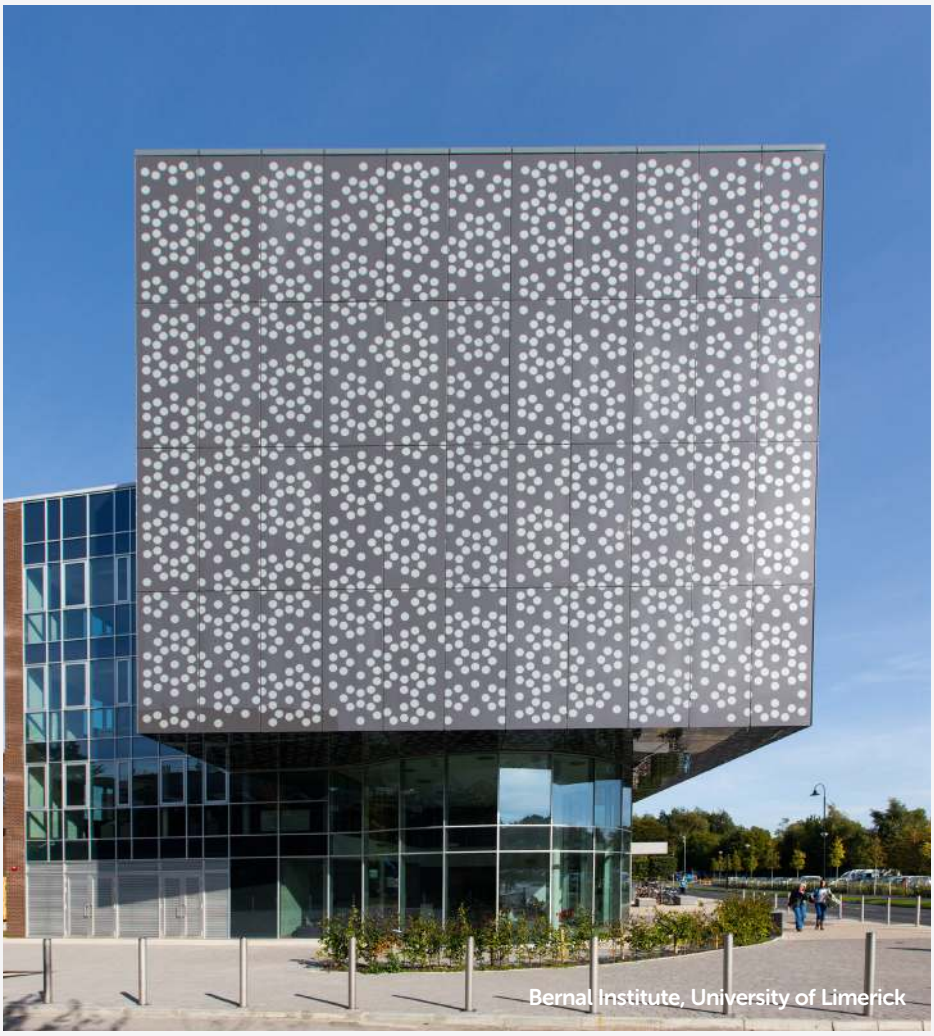
Cracking the code for continuous processing and personalised medicine

Summary of the impact:

Personalised medicine is the next great global challenge for the pharmaceutical industry. The vision of the pharmacy of the future is one in which pharmacies employ disruptive technologies to enable on-demand manufacture of drugs designed to individual needs. For example, multiple medications may be prescribed that treat a patient's exact age-profile and medical history. These medications could then be 3D printed into one tablet, on-demand at the patient's local drug supplier.

Central to this vision is the concept of continuous processing. Currently, active pharmaceutical ingredients (APIs) are manufactured in large batches at distinctly separate times. Continuous processing replaces this large-batch process with the manufacture of lower volumes but at a constant rate. This process enables the continuous flow of product, reduces inventories, and has less batch-to-batch variation, giving higher process control and higher quality.

Researchers led by Prof Gavin Walker at the Bernal Institute, University of Limerick (UL), are generating the chemical engineering solutions for the challenges of personalised medicine. This highly cited research is changing how we train chemical engineers, impacting industry competitiveness, and attracting R&D investment into Ireland.


Bernal Institute, University of Limerick

Underpinning research:

Pharmaceutical manufacturing is a vital facet of the Irish economy. It is responsible for more than 50 percent of exports and employs over 50,000 people directly and indirectly. Over the last ten years, the industry in Ireland has made more than €10,000 million worth of capital investment in facilities. It is a highly advanced sector. In many cases, major companies have made significant repeat investments. This supports the strong reputation that Ireland has built up in this sector, as a country with an excellent regulatory track record and available talent. The Irish-based operations of multinational

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companies (MNCs) are increasingly aware of the need to improve their value proposition to their corporate headquarters. Successful late stage and commercial R&D is highly prized and a signal of long-term investment for Irish MNC operations. Research into engineering solutions that deliver personalised medicine has the potential for world-wide impact on the pharmaceutical industry. This research is a particular ambition for Irish pharmaceutical R&D.

Over the past five years, Professor Gavin Walker, Bernal Chair of Pharmaceutical Powder Engineering, has been tackling the challenge of continuous processing to enable personalised medicine. Prof Walker leads the Bernal Process Engineering Lab at the Bernal Institute, UL, a lab funded by Enterprise Ireland and Science Foundation Ireland. It hosts three national research centres: the Synthesis and Solid State Pharmaceutical Centre (SSPC); the Pharmaceutical Manufacturing Technology Centre (PMTC); the Dairy Processing Technology Centre (DPTC). The award-winning lab[1] is home to an international team of 35 researchers from 12 countries. The purpose-built facility provides a one-of-its-kind environment within Ireland; it is the only academic lab with an industrial scale, fully-ventilated laboratory space and state-of-the-art analytical equipment. Both wet and dry chemistry facilities are available and the lab operates industry-standard quality systems (to the 5S standard). In this environment, industry can be confident the solutions provided meet global standards. In addition, the availability of industrial-size equipment ensures that solutions are brought quickly to the factory-floor. For example, the timeline for Enterprise Ireland research technology transfer from the Lab to Industry is typically 6-12 months.

Furthermore, it is widely recognised across academia and industry that the future manufacture of medicine will be multi-disciplinary. For example, it may involve autonomous, local machines in the corner of a distributing pharmacist or lab, where medicines are printed on-demand to exact medical profiles. Such manufacture requires research at UL to be also multi-disciplinary and this has already begun. UL is leading innovation in crucial areas, such as chemistry (Ref 1, 2), process engineering (Ref 3–7), data analytics (Ref 8), and mathematical modelling (Ref 9).

In addition, given the rise of connected devices and big data, the pharmaceutical industry requires manufacturing systems that have full feedback control or are self-correcting. This requires the lab's research activities to advance process modelling (Ref 10), process analytic technology (PAT) (Ref 11, 12), and statistical modelling (Ref 13), especially for predictive control of pharmaceutical manufacturing (Ref 14, 15). Connected devices and big data also allow medicine manufacturers to reduce the time to market in drug development. The lab's research is improving the efficacy of drug products (Ref, 16, 17) and addresses the special needs of new, more complex active ingredients for specific patient groups (Ref 18 – 20).

As well as contributions to basic research, such as international journal publications, our research has led to the commercialisation of the continuous pharmaceutical manufacturing technologies developed at UL (Ref 21-26). For example, we have created a spin-out UL company Innovative Powder Processing (iP2) that efficiently connects novel academic research to the commercial R&D industry. Through IPP, we have a number of invention disclosures (Ref 27-28) and a patent pending (Ref 29).

References to the research

1. Potter, C.B., Kollamaram, G., Zeglinski, J., Whitaker, D.A., Croker, D.M., Walker, G.M., Investigation of polymorphic transitions of piracetam induced during wet granulation (2017) European Journal of Pharmaceutics and Biopharmaceutics, 119, pp. 36-46. DOI: 10.1016/j.ejpb.2017.05.012
2. Davis, M.T., Potter, C.B., Mohammadpour, M., Albadarin, A.B., Walker, G.M., Design of spray dried ternary solid dispersions comprising itraconazole, soluplus and HPMCP: Effect of constituent compositions (2017) International Journal of Pharmaceutics, 519 (1-2), pp. 365-372. DOI: 10.1016/j.ijpharm.2017.01.043
3. Zhai, H., Li, S., Andrews, G., Jones, D., Bell, S., Walker, G., Nucleation and growth in fluidised hot melt granulation, (2009) Powder Technology, 189 (2), pp. 230-237. DOI: 10.1016/j.powtec.2008.04.021
4. Albadarin, A.B., Potter, C.B., Davis, M.T., Iqbal, J., Korde, S., Pagire, S., Paradkar, A., Walker, G., Development of stability-enhanced ternary solid dispersions via combinations of HPMCP and Soluplus® processed by hot melt extrusion (2017) International Journal of Pharmaceutics, 532 (1), pp. 603-611. DOI: 10.1016/j.ijpharm.2017.09.035
5. Grau-Bove, J., Mangwandi, C., Walker, G., Ring, D., Cronin, K., Studies into the effect of temperature on the impact of model particles in co-melt granulation (2016) Powder Technology, 294, pp. 411-420. DOI: 10.1016/j.powtec.2016.02.041
6. Douglas, P., Albadarin, A.B., Sajjia, M., Mangwandi, C., Kuhs, M., Collins, M.N., Walker, G.M., Effect of poly ethylene glycol on the mechanical and thermal properties of bioactive poly(⊠-caprolactone) melt extrudates for pharmaceutical applications (2016) International Journal of Pharmaceutics, 500 (1-2), pp. 179-186. DOI: 10.1016/j.ijpharm.2016.01.036
7. Douglas, P., Kuhs, M., Sajjia, M., Khraisheh, M., Walker, G., Collins, M.N., Albadarin, A.B., Bioactive PCL matrices with a range of structural & rheological properties, (2016) Reactive and Functional Polymers, 101, pp. 54-62. DOI: 10.1016/j.reactfunctpolym.2016.02.004
8. Sajjia, M., Shirazian, S., Kelly, C.B., Albadarin, A.B., Walker, G., ANN Analysis of a Roller Compaction Process in the Pharmaceutical Industry (2017) Chemical Engineering and Technology, 40 (3), pp. 487-492. DOI: 10.1002/ceat.201600229
9. Shirazian, S., Kuhs, M., Darwish, S., Croker, D., Walker, G.M., Artificial neural network modelling of continuous wet granulation using a twin-screw extruder (2017) International Journal of Pharmaceutics, 521 (1-2), pp. 102-109. DOI: 10.1016/j.ijpharm.2017.02.009
10. Kuhs, M., Moore, J., Kollamaram, G., Walker, G., Croker, D., Predicting optimal wet granulation parameters for extrusion-spheronisation of pharmaceutical pellets using a mixer torque rheometer (2017) International Journal of Pharmaceutics, 517 (1-2), pp. 19-24. DOI: 10.1016/j.ijpharm.2016.11.057
11. Walker, G.M., Bell, S.E.J., Greene, K., Jones, D.S., Andrews, G.P., Characterisation of fluidised bed granulation processes using in-situ Raman spectroscopy, (2009) Chemical

[1] Winner of Irish Chemical Lab of the Year, Irish Pharmaceutical Lab, Academic Laboratory Award of the Year 2017.

Engineering Science, 64 (1), pp. 91-98. DOI: 10.1016/j.ces.2008.09.011
12. Walker, G., Bell, S.E.J., Vann, M., Jones, D.S., Andrews, G., Fluidised bed characterisation using Raman spectroscopy: Applications to pharmaceutical processing (2007) Chemical Engineering Science, 62 (14), pp. 3832-3838. DOI: 10.1016/j.ces.2007.04.017
13. Sajjia, M., Albadarin, A.B., Walker, G., Statistical analysis of industrial-scale roller compactor 'Freund TF-MINI model', (2016) International Journal of Pharmaceutics, 513 (1-2), pp. 453-463. DOI: 10.1016/j.ijpharm.2016.09.052
14. Shirazian, S., Darwish, S., Kuhs, M., Croker, D.M., Walker, G.M. Regime-separated approach for population balance modelling of continuous wet granulation of pharmaceutical formulations, (2018) Powder Technology, 325, pp. 420-428. DOI: 10.1016/j.powtec.2017.11.047
15. Sajjia, M., Shirazian, S., Egan, D., Iqbal, J., Albadarin, A.B., Southern, M., Walker, G., Mechanistic modelling of industrial-scale roller compactor 'Freund TF-MINI model' (2017) Computers and Chemical Engineering, 104, pp. 141-150. DOI: 10.1016/j.compchemeng.2017.04.018
16. Crawford, D.E., Miskimmin, C.K.G., Albadarin, A.B., Walker, G., James, S.L., Organic synthesis by Twin Screw Extrusion (TSE): Continuous, scalable and solvent-free (2017) Green Chemistry, 19 (6), pp. 1507-1518. DOI: 10.1039/c6gc03413f
17. Davis, M.T., Egan, D.P., Kuhs, M., Albadarin, A.B., Griffin, C.S., Collins, J.A., Walker, G.M. Amorphous solid dispersions of BCS class II drugs: A rational approach to solvent and polymer selection (2016) Chemical Engineering Research and Design, 110, pp. 192-199. DOI: 10.1016/j.cherd.2016.04.008
18. Kollamaram, G., Hopkins, S.C., Glowacki, B.A., Croker, D.M., Walker, G.M., Inkjet printing of paracetamol and indomethacin using electromagnetic technology: Rheological compatibility and polymorphic selectivity, (2018) European Journal of Pharmaceutical Sciences, 115, pp. 248-257. DOI: 10.1016/j.ejps.2018.01.036
19. Ziaee, A., Albadarin, A.B., Padrela, L., Faucher, A., O'Reilly, E., Walker, G., Spray drying ternary amorphous solid dispersions of ibuprofen – An investigation into critical formulation and processing parameters, (2017) European Journal of Pharmaceutics and Biopharmaceutics, 120, pp. 43-51. DOI: 10.1016/j.ejpb.2017.08.005
20. Castro-Dominguez, B., Moroney, K., Schaller, B., O'Connor, S., Cloonan, A., Vo, T.T.N., Walker, G., O'Reilly, E.J., Electrospun API-loaded mixed matrix membranes for controlled release, (2017) RSC Advances, 7 (68), pp. 43300-43309. DOI: 10.1039/c7ra08600h
21. Albadarin, A.B., Zeglinski, J., Walker, G., "A method of processing active pharmaceutical ingredients and apparatus for use in such methods", Patent Application P34678GB1 (2018)
22. Pishnamazi, M., Iqbal, J., Shirazian, S., Walker, G.M., Collins, M.N., Effect of lignin on the release rate of acetylsalicylic acid tablets (2019) International Journal of Biological Macromolecules, 124, pp. 354-359. DOI: 10.1016/j.ijbiomac.2018.11.136
23. Ismail, H.Y., Singh, M., Darwish, S., Kuhs, M., Shirazian, S., Croker, D.M., Khraisheh, M., Albadarin, A.B., Walker, G.M., Developing ANN-Kriging hybrid model based on process parameters for prediction of mean residence time distribution in twin-screw wet granulation (2019) Powder Technology, 343, pp. 568-577. DOI: 10.1016/j.powtec.2018.11.060
24. Szewczyk, A., Prokopowicz, M., Sawicki, W., Majda, D., Walker, G., Aminopropyl-functionalized mesoporous silica SBA-15 as drug carrier for cefazolin: adsorption profiles, release studies, and mineralization potential (2019) Microporous and Mesoporous Materials, 274, pp. 113-126. DOI: 10.1016/j.micromeso.2018.07.046
25. Ziaee, A., Albadarin, A.B., Padrela, L., Femmer, T., O'Reilly, E., Walker, G., Spray drying of pharmaceuticals and biopharmaceuticals: Critical parameters and experimental process optimization approaches, (2019) European Journal of Pharmaceutical Sciences, 127, pp. 300-318. DOI: 10.1016/j.ejps.2018.10.026
26. Pishnamazi, M., Casilagan, S., Clancy, C., Shirazian, S., Iqbal, J., Egan, D., Edlin, C., Croker, D.M., Walker, G.M., Collins, M.N., Microcrystalline cellulose, lactose and lignin blends: Process mapping of dry granulation via roll compaction (2019) Powder Technology, 341, pp. 38-50. DOI: 10.1016/j.powtec.2018.07.003
27. Invention Disclosure: J Zeglinski, AB Albadarin, G Walker, B Wood, Continuous drying of active pharmaceutical ingredients in twin screw extruder, UL Invention Disclosure (July 2017)
28. Invention Disclosure: AB Albadarin , J Zeglinski, G Walker, Continuous wet granulation-coupled in situ drying in twin screw granulator for pharmaceutical production, UL Invention Disclosure (July 2017)
29. AB Albadarin, J Zeglinski, G Walker, "A method of processing active pharmaceutical ingredients and apparatus for use in such methods", P34678GB1 (priority patent)

Grants and Awards

The group are recipients of several national and international awards:

Enterprise Ireland, Pharmaceutical Manufacturing Technology Centre (PMTC), Phase 1, €6 million (2014-2019)

Science Foundation Ireland IvP, "Model predictive control of pharmaceutical processing", €0.95 million (2014-2019)

Engineering and Physical Sciences Research Council (EPSRC) UK, "Synthesis by extrusion", €0.6 million (2014-2018)

Science Foundation Ireland Spoke Award SSPC, "Momentum", €1.9 million (2014-2019)

Enterprise Ireland, IPP, "Biopharmaceutical powder flow processing", €0.2 million (2015-2017)

National Science Foundation/Science Foundation Ireland, US-Ireland R&D Partnership Programme, "Nano-medicines", €1.3 million (2015-2019)

Enterprise Ireland IPP, "Advanced formulation development", €0.65 million (2015-2017)

Science Foundation Ireland, SIRG Starting Investigator Research Grant (SIRG) (15/SIRG/3552): Natural matErials for Advanced Therapeutics (NEAT), €0.5 million (2016-2020)

European Commission, H2020 MSCA-Co-Fund, "PROCESS", €1.9 million (2018-2021)

Enterprise Ireland, Pharmaceutical Manufacturing Technology Centre (PMTC) Phase 2, €6 million (2019-2024)

National awards arising from the research include: Irish Lab Award: Chemical Lab of the Year (2017); Pharmaceutical Lab of the Year at the Irish Lab Awards (2017); Research-Academic Lab of the Year (2017).

Details of the impact

Three of the most important impacts from this body of research are on industry through disruptive technologies driving innovation and growth, regional R&D through increased investment, and academia through new programmes and more informed practice.

Prof Walker and his team have forged long-standing partnerships with industry that, through PMTC and SSPC, have led to new product developments, greater efficiencies, and quality standards across multinational and SME firms. New technologies that PMTC implements, in close cooperation with other enterprises, MNCs and PMTC, also enable SMEs to strengthen their capacity and ability to drive innovation through research and development (R&D). PMTC enables SMEs to be part of a cluster or ecosystem of companies, clients and researchers. This membership reduces the barriers to innovation, collaboration and R&D and provides a neutral ground for meeting clients and suppliers.

For example, Luke Kiernan of the Irish SME Innopharma Labs states that, for their successful European Commission SME award of €2.3 million, "Innopharma labs have benefitted from our strong involvement in Prof Walker's group and having an academic case study on a successful continuous pharmaceutical processing was extremely useful for our successful H2020 submission". (Source 1)

Through the SSPC MOMEnTUM Spoke project hosted by the Bernal Process Engineering Laboratory, the team are working closely with leading corporate technical staff from Johnson & Johnson, linking sites across 4 countries: Puerto Rico, US, Belgium, and France. This collaboration is described as "the foundational enablement for manufacturing of the future" with impacts on understanding of science and engineering in the development of emerging technologies which supports industry to become more innovative. (Source 2)

The research findings inform professional training and quality standards in the pharmaceutical industry. Prof Walker and Dr Albadarin have contributed to the establishment of the Specialist Diploma in Regulatory Affairs, a diploma developed with input from the Health Products Regulatory Authority and BioPharmaChem Ireland experts. The programme is developed in response to industry need and a strong demand in Ireland for regulatory affairs professionals for the pharmaceutical industry. Through a series of masterclasses, the team contributes to upskilling the Irish pharmaceutical sector, instilling a better understanding of patient impact.

Greg Donegan, senior scientist at Roche, explains: "Coming from a drug substance background and with little to no exposure of the concepts and issues faced in the drug product world", taking Industrial Pharmaceutical Master Classes facilitated by Prof Walker's Bernal Process Engineering Laboratory he "gained a lot of understanding about how drug product formulation is crucial to patients' wellbeing. This was shown both theoretically in the presentations and practically with the demonstrations of different types of equipment".

He adds that "some of the PAT techniques were particularly interesting", especially as PAT "plays an important role for us in the drug substance part of Roche". (Source 3)
PMTC's impact on technological innovation in industry, regional investment, and academia will continue and deepen through its recently-awarded MCSA/ European Commission co-funded fellowship programme PROCESS. PROCESS is a five-year programme with the overall theme of advanced manufacture of high value products and engineering solutions for related industries. Its particular emphasis is on particulate product processing for new products in the dairy and pharmaceutical sectors. The programme is envisaged to be multi-disciplinary, for example, including process modelling and smart data management, and international, recruiting up to 26 research fellows from several nationalities. It also engages with the larger industry and academic community outside UL, requiring fellows to take secondments in the dairy and pharmaceutical businesses as well as other related research centres.

Sources to corroborate the impact

1. Luke Kiernan, Technology Director and H2020 co-ordinator, Innopharma Labs, Irish SME
2. Carlos Escobar Rodriguez, Senior Director Enterprise Manufacturing Engineering & Technology, Johnson & Johnson Product Supply, Puerto Rico.
3. Greg Donegan, Senior Scientist, Roche, Clarecastle, Ireland on Industrial Pharmaceutical Master Classes facilitated by Prof Walker's Bernal Process Engineering Laboratory

Find out more: Listen to the podcast and read other impact case studies www.ul.ie/researchimpact

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