SSPC

The SFI Research Centre for Pharmaceuticals

A World Leading SFI Research Centre

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RESEARCHER CASE STUDIES

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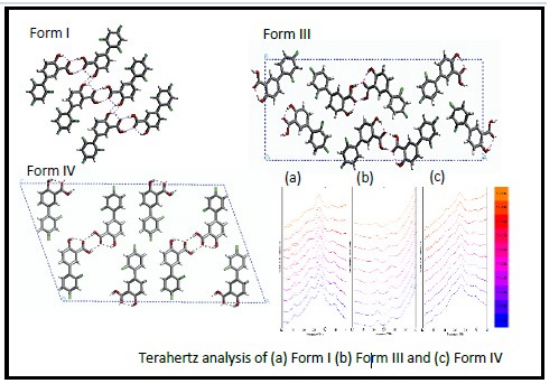
Francesco Civati, SSPC Graduate of the Year 2019
NUI Galway, sponsored by Eli Lilly

This award recognises Francesco Civati, NUI Galway, for being an exceptional SSPC PhD graduate based on his PhD achievements and outputs. Francesco was supervised by Andrea Erxleben and his PhD was based on Control of polymorphism, crystal size and habit in pharmaceuticals. Thank you to Eli Lilly for sponsorship.

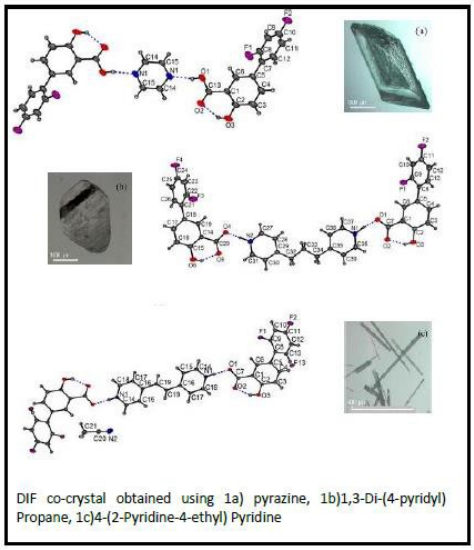
Introduction

Solid state characteristics of an Active Pharmaceutical Ingredient (API), generally define a wide range of properties such as polymorphism and morphology. These characteristics contribute significantly to the arrangement of molecules in space. To an extent, it is possible to modify molecular organization while selectively targeting these properties. The aim of my research is to study the polymorphism and morphology of API's during the manufacturing process and investigate the possibility of selectively altering these characteristics of the solid material. Control of both characteristics can lead to the formation of more effective and affordable medications.

Each polymorphic forms of a material can have different bioavailability to the other polymorph, therefore during production, it is important to obtain the same form in a robust and reproducible manner. One of the main problems is that solid materials can change between polymorphic forms at any time during manufacturing. Identification of the point where these transformations occur poses a major challenge to industry. For this reason, we have developed a method to study the spectroscopic characteristics of different polymorphs of the API diflunisal. We have also developed a robust method to produce the most stable polymorphic form of the API.



Terahertz analysis of (a) Form I (b) Form III and (c) Form IV


DIF co-crystal obtained using 1a) pyrazine, 1b)1,3-Di-(4-pyridyl) Propane, 1c)4-(2-Pyridine-4-ethyl) Pyridine

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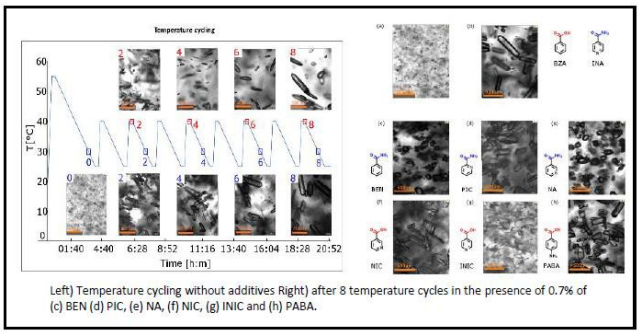
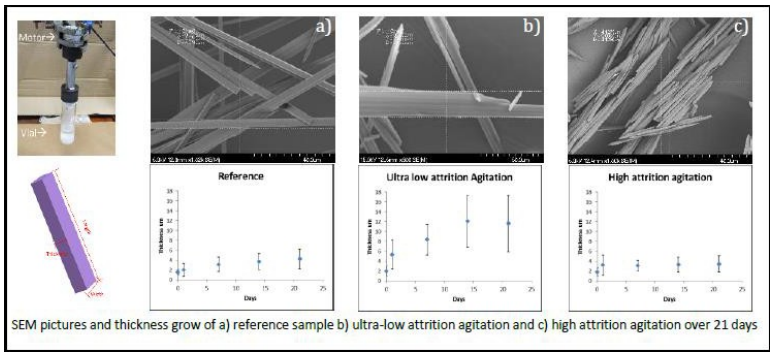
In another case study, crystal habit modification was achieved using a combination of temperature cycling and substitution of additives. The selected target benzoicacid isonicotinamide co-crystals were subjected to a temperature cycling process. This technique showed a drastic alteration in the crystal dimensions and in three cases a change in morphology. The combined effects of addition of tailor-made additives, and temperature cycling, formation of more processable crystals was achieved.



Left) Temperature cycling without additives Right) after 8 temperature cycles in the presence of 0.7% of (c) BEN (d) PIC, (e) NA, (f) NIC, (g) INIC and (h) PABA.

Lastly, a high shear ultra-low attrition agitation (HSULAA) process for solid-state modification of needle crystals was developed. This method allowed needle-like crystals to grow to a more filterable shape without breaking. During this process, the HSULAA was used to transform gel-forming needles to a more easily filterable crystal shape. The method involved the use of rapid sample spinning with rapid spin-direction reversal. This generated high shear in the crystal/solution mixture which accelerated the Ostwald ripening of the crystals.



SEM pictures and thickness grow of a) reference sample b) ultra-low attrition agitation and c) high attrition agitation over 21 days

SSPC's contribution to the PhD experience:

Intersectoral Networking

My career goal is to be a well rounded researcher and to bridge the industrial and academic worlds. Through SSPC, I was able to gain experience in both work environments: over the course of my PhD. I was able to enrol in an industry-related project in collaboration between NUIG, UL and Roche. During this time, I gained valuable industry experience and I further developed my critical thinking and problem-solving skills with the supervision of an industrial tutor. I was able to independently develop a prediction method which to be used in the manufacturing process and advance the performance of the final product This experience allowed me to enhance my understanding of crystal engineering as well as develop a comprehensive overview of the research field.

Outreach

SSPC recognises the importance of outreach and public engagement : researchers are encouraged to give back to the community and increase the understanding of the research by non-scientists. I was empowered by the importance placed on outreach by the SSPC community and thoroughly enjoyed being able to contribute. I have always believed education should be free and fair for everyone, and this vision is shared by the SSPC community.

Over the course of my PhD I was encouraged to act as role model and take a leadership position in organizing outreach showcase at events such as the BT young scientist exhibition in Dublin and Galway technology festival. I was afforded the opportunity to communicate my research to a young and enthusiastic audience and take part in events directed towards the general public such as Fame Lab and Threesis, where I could convey my research to the general public, transmitting the importance of the work being carried out in the cluster as well as the wider implications for society. I found the appreciative attitude of the SSPC towards outreach to be a strong motivating factor in seeking out new ways to interact with non-scientists who also shared my enthusiasm.

Extraordinary research facilities/ collaborative environment

Over the course of my PhD I undertook research that had significant implications on a wide range of pharmaceutical applications. Through productive collaborations with both academic and industrial partners. The discoveries that I have made can have an impact and they can be used to ensure the public has access to less expensive more effective and potent medications. SSPC gave me the necessary tools to enhancing my understanding of pharmaceutical chemistry as well as a solid collaborative platform in which I could have experience the best research possible

Three major outputs of my PhD are:

Industrial collaboration between SSPC (NUIG and UL) and Roche:

In this collaborative project I was able to produce cutting edge research and apply my skills to a highly relevant API that is already commercially available.

Collaboration between CMAC and SSPC:

To carry out a final investigation of my project I was encouraged to write a grant proposal that allowed me to travel to the CMAC centre. I was able to lead a study on the effect of additives on needle-like co-crystals. The choice of research centre at an impactful stage of my career and gave me the opportunity to establish a connection between the two centres.

Scientific dissemination:

During my doctoral studies, I was able to build a strong track record of research and results which allowed me to present my work at national and international conferences. My PhD was completed in four years and produced three articles already published in accredited journals with two more in the process of submission. I had a leading role in all the work performed and I contributed extensively to the published material, not only by actually carrying out the experimental work, but also enhancing the research with new ideas inspired by thoughtful contributions from my collaborators.

Publication List

-F. Civati, A. Erxleben, P. McArdle. The Role of H-bonding and Molecular Stacking in the Growth of Needle Crystals. Manuscript under preparation.

- F. Civati, V. Svoboda, S. Urwin, P. McArdle, A. Erxleben, D. Croker, J.H. ter Horst. Manipulating co-crystal size and morphology using a combination of temperature cycling and additives. Manuscript under preparation.

-F. Civati, A. Erxleben, S. Kellehan, P. McArdle. Conversion of gel-forming crystal needles to easily processable more equant crystals using high-shear-ultra- low-attrition agitation: Accelerated Ostwald ripening without crystal attrition. Cryst. Growth Des. 2019, 19, 1502-1504.

-A. R. Pallipurath, F. Civati, J. Sibik, C. Crowley, J. A. Zeitler, P. McArdle and A. Erxleben. A. Comprehensive Spectroscopic Study of the Polymorphs of Diflunisal and their Phase Transformations. Int. J. Pharm. 2017, 528, 312-321.

-A. R. Pallipurath, F. Civati, M.Eziashi, E. Omar, P. McArdle, and A. Erxleben. Tailoring Cocrystal and Salt Formation and Controlling the Crystal Habit of Diflunisal. Cryst. Growth Des. 2016, 16, 6468-6478.

SSPC SSPC Industrial PhD Placement Award sponsored by MSD
Barry Long, University of Limerick

Barry Long, received this award for showing an exceptional and impactful SSPC PhD placement experience, an award sponsored by MSD.

Barry's PhD title is Supercritical Enhanced Atomization – A novel spray drying process for the continuous generation and drying of nanoparticles using supercritical methods, supervised by Kevin Ryan and Luis Padrela and Patrick Faulkner, MSD.

MSD have been partnering with SSPC since 2009 and through this partnership have advanced knowledge and 'know how' on site particularly in the area of Crystallisation. Membership with SSPC has helped to strengthen the Irish manufacturing operations as it positions itself to continue to move up the value chain and compete globally for R&D projects.

A key impact of SSPC is the creation of a unique talent pipeline with the transition rate of SSPC researchers to industry currently standing at 70%. One of the key drivers facilitating the high number of transitions to industry is the SSPC PhD industry placement programme, which brings students into the industrial environment for a three-month placement aligned with their research area. This exposes researchers to the realities of industrial processing while simultaneously providing industry with an insight into current research innovations.

MSD has hosted six SSPC PhD students to date and the placement programme has proven very beneficial to all parties facilitating knowledge exchange and upskilling between both student and staff. The exposure to cooperative mentoring by industrial members provides students with experience in project management, problem-solving and develops the skills needed to communicate research to various audiences. The supplementary training that SSPC students receive during their placements ensure that our graduates have industrially-relevant skills to support the pharmaceutical and biopharmaceutical industry.

Barry Long, was placed at MSD Ballydine in 2019 and after his time in MSD his opinion on industry has completely changed.

"In 2017, MSD invested €40 million in a new spray drying facility at Ballydine. As my PhD involves spray drying, it was great to be able to work in a company that had recently invested in a spray dryer as I was able to learn at the perfect pace. Before my placement, I had some experience in a supplier quality and regulatory compliance role which made me think industry, consisted of paperwork only!

The majority of my time at MSD was spent working on the spray dryer but I was lucky enough to have the opportunity to witness the other operations that took place on site, from API manufacture to tabletting to physical characterisation of materials. This provided me with a good idea of how life in the pharmaceutical industry typically goes from day to day. I was delighted that I was able to complete work that was relevant to my PhD as well as understand new processes, helping expand my experience.

The major differences I found between industry and academia involved the level of planning and understanding. Unlike academia, it is not possible to be able to decide what your plan is at the start of each day and, instead, weeks if not months of planning is required for each bit of work undertaken. The time I spent in MSD has completely changed my perspective and as I get closer to graduation, I hope to, one day, make the move to industry and who knows maybe even back to MSD."

"MSD has hired a number of PhD graduates from SSPC and intends to hire more in the future. Many of the PhD students in the SSPC who have been exposed to the innovative and applied research projects with industry along with the new technologies at the SSPC are well positioned to take up these positions in companies like MSD."
Tom O'Ceallaigh, Director of Engineering, MSD

SSPC Education & Public Engagement Champion of the Year
Shubhangi Kakkar, University of Limerick

The EPE Champion of the Year goes to someone who has demonstrated commitment to and flair for public engagement and outreach in 2019.

Dr Shubhangi Kakkar, finished her PhD journey with SSPC in June this year, during lockdown. Her research included looking at how the active ingredients in drugs form crystals in liquids. "Crystallisation is important for making and formulating many medicines, and I looked at the first step in the formation of these crystals and analysed how these molecules of the drug's active ingredient cluster together."

Being part of a Science Foundation Ireland (SFI) funded research centre, Shubhangi had opportunity to engage with the Education and Public Engagement (EPE) team. For her, public engagement has enriched her teaching and learning abilities. It has helped her understand the importance of public speaking and how to handle a crowd as a speaker of Pint of Science.

Shubhangi said taking part in the public engagement activities has developed her transferable skills such as her leadership qualities and communication skills, while explaining her work and its social implications to the society. With these activities, she has directed her knowledge flow to help build a more sustainable and healthy society. She feels like she is now connected to society.

"Even during the preparation of this presentation, I had so much fun. I could have never thought in my life to do this if was not with SSPC Education and Public Engagement (EPE) activities. But now I want to do it every year."

Shubhangi enjoyed working with students because she was able to demonstrate her abilities without the fear of being judged, while also further developing her life skills and social networking skills. She found these activities were such fun and sometimes even challenge her academic thinking as it points out how we complicate such simple things with our knowledge.

"These activities feel like we are making a difference in society and not just sitting at our computer screens working towards PhD goal."

Whilst demonstrating and teaching in public engagement activities Shubhangi represented SSPC, which helps society to know more about our organization and the opportunities in it. The activities that she has done in schools, museums and workshops in Universities have helped the public to know about how SSPC works and all our processes.

Shubhangi has completed an outstanding 14 activities in 1 year, and added:

"This past year was special as I had completed my goal for 4 EPE activities at the start of the year, which was highly rewarding and gave me a lift to complete 14 activities in 1 year especially when doing these activities is like an adrenaline boost for a person like me."

SSPC Academic Collaboration of the Year sponsored by IRDG
Ana Luiza Pinto Queiroz, University College Cork

This award is in recognition of collaborative projects between academics at different institutions within SSPC's higher education partners, that have yielded outputs that would not have been possible without the involvement of both/more.

The collaboration included support from members at University college Cork (UCC), University of Limerick (UL), University College Dublin (UCD) and Trinity College Dublin (TCD). Abina Crean, Sonja Vucen (UCC), Barbara Schaller (UL), Barbara Wood, (UCD) & APC Ltd., Anne Marie Healy (TCD) and Jayprakash Yadav (TCD).

The project entitled "Investigating relationships between microcrystalline cellulose crystallinity and moisture sorption capacity" was led by the PhD candidate Ana Luiza P. Queiroz, her supervisor Dr Abina Crean, and co-supervisor Dr Sonja Vucen. The aim of this study was to firstly develop an analytical technique to rapidly quantify Microcrystalline cellulose (MCC) crystallinity and to secondly assess the relationship between MCC crystallinity and moisture sorption. Then apply the findings to control granulation and tabletability process parameters and predict tablet dissolution behaviour. MCC is the excipient most widely used in solid dosage forms. It is a semi-crystalline material with inherent crystallinity variability due to raw material source and variable processing conditions. If not well controlled, the variability of this critical material attributes may negatively impact on control of processes (granulation, tabletting) as well as the critical quality attributes of final products.

Nature of Collaboration

The initial experimental work was carried out by Ana Luiza at UCC. However, it became apparent that the most suitable analytical instrumentation was not available in UCC. Therefore, Ana Luiza reached out to academic and industry researchers in other partner institutes and companies.

As an Oscillatory ball mill and Raman MR probe were located at UL, additional experimental work was performed at the Bernal Institute with access organized by postdoctoral researcher Barbara Schaller. In addition, Dr Barbara Wood, postdoctoral researcher at UCD at the time, now Research Fellow at APC Ltd., organized access to Ana Luiza to use advanced disintegration and dissolution PAT tools in UCD (Easymax® system with FBRM® and PVM® probes). Barbara also organized access to Ana Luiza to use a Raman PhAT probe at APC Ltd. However, Ana Luiza realized that the Raman PhAT probe in place was not functioning with the required sensitivity and the experimental work involving this technique had to be put in standby.

With follow up, Prof. Anne Marie Healy, TCD, organized access to Ana Luiza to use TCD's Raman PhAT probe. In turn, Ana Luiza also provided training to TCD researchers on how to operate the system, troubleshoot and analyse the Raman spectroscopy data obtained.

Licence

The application called McCrystal (an RShiny app.) was designed based on the research and is now available on the SSPC website (www.sspc.ie). This serves as a guide other SSPC researchers about how modelling research can be disseminated.

Ana Luiza was offered a contract as a Process Development Engineer at APC Ltd, in April 2020. Part of this achievement was due to the expertise gained while Ana Luiza was doing the experimental work mentioned above in UCD and APC Ltd.

"The achievements of this project could have been achieved without this collaboration within SSPC, demonstrating a very positive Centre Effect. The team would like to thank SFI for funding the SSPC Centre, and SSPC Operations Team for encouraging this collaborative environment between academics and industry partners". Ana Luiza Pinto Queiroz.

SSPC Industry Impact of the Year
Ahmad Ziaee, University of Limerick sponsored by BPCI

Dr Ahmad Ziaee is acknowledged for his research outputs that have made a tangible impact with/for an industrial partner. An award sponsored by Biopharmachem Ireland (bpci).

MOMEnTUM
SSPC SPOKES PROJECT

Ahmad's research was based on Spray Drying of Pharmaceuticals and Biopharmaceutical: Optimization of Process and Formulation, supervised by Dr Emmet O'Reilly and Prof. Gavin Walker, working with SSPC's MOMENTUM project, the first single industry partner project between Johnson and Johnson (J&J) and SSPC, jointly funded by Science Foundation of Ireland (SFI) and J&J.

As pharma and biopharma industry are transitioning from batch to continuous processes, demand of replacing batch processes such as freeze drying (time consuming, expensive) with continuous processes such as spray drying (SD) (cheap, highly controllable and efficient) has been seen within the industrial community. Therefore, MOMENTUM project was funded with the focus of enabling SD of pharmaceuticals and biopharmaceuticals to improve the stability and dissolution rate of large and small molecule active pharmaceutical ingredients (APIs) via continuous process.

The project kicked-off with drafting a collaborative literature review paper with collaborators in Janssen, Belgium on SD of pharmaceuticals and biopharmaceuticals which has been published in European Journal of Pharmaceutical Sciences. The review paper covers the state-of-the-art process and formulation experimental optimization approaches for SD of small and large molecule APIs.

The first phase of the project was in collaboration with Janssen in Belgium to optimize the process and formulation factors of spray drying of small molecule APIs with low aqueous solubility. The candidate API was formulated as amorphous solid dispersion (ASD) while the SD process was optimized using a design of experiment (DoE) approach. The work was orally presented in AIChE 2016 in San Francisco and published in European Journal of Pharmaceutics and Biopharmaceutics.

In an attempt to SD large molecule APIs, lysozyme was selected as a candidate molecule. DoE approach in combination with forced deactivation studies was introduced as an efficient strategy for SD of large molecule APIs. The results led to another collaborative paper with our industry partner published in the journal of Powder Technology in addition to an oral presentation at EuPAT9, 2018 conference in Manchester.

SSPC Industry Impact of the Year
Ahmad Ziaee, University of Limerick sponsored by BPCI

The success of the last two phases of the project set the basis for cooperation with parenteral centre of innovation of Janssen in Switzerland. This included J&J's in-kind contribution of monoclonal antibodies (mAbs). The DoE approach was carefully designed and implemented using the BUCHI B290 in powder processing lab. Samples were characterized using resources available in Bernal biolabs, chemical sciences department and powder engineering labs in Bernal Institute, UL. The results showcased our capabilities in optimizing the SD process of large molecule APIs as a comparable technology to the freeze drying which is the benchmark drying process in biopharmaceutical sector. Our collaboration has been continued even after my PhD viva in November 2019 by working on drafting our next collaborative publication on SD of mAb.

During the 3.5 year of his PhD, Ahmad had opportunity to attend in more than 70 teleconference and face-to-face meetings with our industrial partners from Janssen Puerto Rico, Belgium and Switzerland.

His first introduction to SSPC was when he was still a master by research student under supervision of Prof. Michael Zaworotko and Dr. Syed Tofail back in 2015:

"I still remember it clearly that as an outsider I was always amazed by the level of positive communication and learning opportunities within the centre."

This continued under the supervision of Prof. Gavin Walker, SSPC co-director and Dr Emmet O'Reilly. Prof. Gavin Walker is the Bernal chair of pharmaceutical powder processing with immense experience in process optimization. Working in his group exposed Ahmad to a friendly and highly professional environment. Working with Dr Emmet O'Reilly with his open-door policy, patience and great chemistry knowledge was an immense opportunity for catalysing the progress of Ahmad's research.

Moreover, the presence of a project manager, Ms. Aisling Arthur in MOMENTUM project, Ahmad said,

"Introduced him to the basics of time management, meeting milestones and deliverables. Also, being able to use the SSPC state-of-the-art labs in Bernal institute was a huge advantage of being part of the centre."

Ahmad is now a postdoctoral researcher at Bernal Institute, University of Limerick.