Institution: University of Cambridge

Unit of Assessment: 8 - Chemistry

Title of case study: Liquid Assisted Grinding

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

Research by Professor Jones, Department of Chemistry, University of Cambridge, resulted in the development of a new method for preparing composite solids, involving the grinding of two or more crystalline solids in the presence of small volumes of liquid. This so called "liquid assisted grinding" (LAG) which produces novel solids with bespoke physical and chemical properties, is now routinely used by the major pharmaceutical companies to screen for new drug forms as part of their drug product development process.

2. Underpinning research (indicative maximum 500 words)

Liquid Assisted Grinding (LAG) was developed by Prof William Jones who has been employed as a member of staff in the Chemistry Department, University of Cambridge, since 1978 (SAIR, 1978; ADR 1985; Reader, 1999; Professor, 2006 onwards) and leads a research group focused on Materials Chemistry. The discovery of LAG as an effective screening method was made in 2001 and published in the Royal Society of Chemistry journal Chemical Communications in 2002.[1] This work demonstrated how the kinetics of the solid-solid reaction could be accelerated. Prior to this work solution crystallisation was the main method of doing solid form screening.

The discovery resulted from work in the Jones Group on understanding how organic molecules pack and interact in the solid state. To expand in a systematic way the number and types of interactions that were possible between molecules within an organic crystal structure, from 1995 onwards the Jones Group investigated methods for preparing crystalline solids with two or more distinct molecular entities within them.[2] This meant, for example, that to understand how an acid function interacted with an amine function in a crystal lattice, it was not necessary to have both functionalities present on the same molecule. To obtain such multicomponent solids is difficult if the solubility of the two molecules which are being co-crystallised is very different – they will simply crystallise as separate pure phases.

Solid-state grinding had been explored previously by others for producing co-crystals, but in 2001 the Jones Group embarked on a series of studies to see whether a small amount of liquid added to the solids during mixing could have an effect on the outcome. It was discovered in 2001 that not only did small amounts of liquid speed up the solid-solid reaction but in numerous cases it allowed the formation of new solid forms that could not otherwise be made. The method has now been termed "liquid assisted grinding". The group disclosed this discovery in 2002 where the enhanced kinetics was noted.[1] Between 2002 and 2005 the Jones Group discovered that the exact outcome of the solid state grinding could be controlled by careful choice of the added liquid.[3] Between 2005 and 2007 it was further demonstrated that this LAG approach is significantly more effective in searching for alternate solid forms of drug candidates than other previously used methods, e.g. conventional solution crystallisation or melt growth.[4&5] LAG is a method that requires very small amounts of material, essential for preformulation pharmaceutical development, is rapid, and environmentally friendly because it eliminates the need to use large amounts of solvents.

A recent independent study comparing the effectiveness of the various approaches to screening for new forms of the drug piroxicam is given by Fucke, et al (2012).[6] The authors conclude that: "*Solvent-drop grinding showed the highest absolute number of experiments resulting in co-crystals*" and ""*For an initial screening solvent drop grinding should be preferred, as this method produced reliably co-crystal forms*."

In the pharmaceutical industry many drug candidates in their pure form suffer from very poor physical and chemical attributes. An example is the increasingly common problem of poor solubility

and bioavailability. To improve solubility the pharmaceutical industry routinely searches for alternative solid forms of the drug, e.g. formation of salt and/or co-crystal forms. The prior established practice of screening by conventional crystallisation from solution is particularly difficult because drug and coformer will tend to crystallise separately.

The LAG research was supported by Pfizer grants. The following staff members working in the Jones Group contributed to the underpinning research: Delia Haynes (PDRA 2002-2005) and Tomislav Frisic (PDRA 2005-2007). Additionally, Dr Sam Motherwell from the Cambridge Crystallographic Data Centre (1992–present) provided database support; and Professor Fumio Toda (Matsuyama, Japan (deceased)) provided background information on solid-solid grinding. Members of the Jones Group also included PhD students Ning Shan (PhD 2000-2003), Andrew Trask (PhD 2002 -2005) and Shyam Karki (PhD 2006 -2009).

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

1. Shan, N., Toda, F., & Jones, W. (2002) Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. *Chemical Communications*, 2372- 2373. (*****)
2. Batchelor, E., Klinowski, J., & Jones, W. (2000) Crystal engineering using co-crystallisation of phenazine with dicarboxylic acids. *Journal of Materials Chemistry,* 10: 839–848.
3. Trask, A. V., van de Streek, J., Motherwell, W. D. S., & Jones, W. (2005) Achieving Polymorphic and Stoichiometric Diversity in Cocrystal Formation: Importance of Solid-State Grinding, Powder X-ray Structure Determination, and Seeding. *Crystal Growth & Design*, 5 (6), 2233-2241. (*****)
4. Karki, S., Friscić, T., Jones, W., & Motherwell, W. D. S. (2007) Screening for pharmaceutical cocrystal hydrates via neat and liquid-assisted grinding. *Molecular Pharmaceutics* 4 (3): 347–354. (*****)
5. Trask, A. V., Haynes, D. A., Motherwell, W. D. S., & Jones, W. (2006) Screening for crystalline salts via mechanochemistry. *Chemical Communications*, 51–53.
6. Fucke, K., Myz, S. A., Shakhtshneider, T. P., Boldyreva, E. V., and Griesser, U. J. (2012) How good are the crystallisation methods for co-crystals? A comparative study of piroxicam. *New Journal of Chemistry* 36, 1969-1977.

(*****) References that best indicate the quality of the research.

Grant Information

- Grant No: RG34605 MAAG/163; PI: Prof W Jones; Grant Title: Ab initio structure prediction; Sponsor: Pfizer; Period of Grant: 2002-2003; Value of Grant: £289,173
- Grant No: RG44738 MAAG/411; PI: Prof W Jones; Grant Title: Cocrystal design for non-polar (weak synthon) molecules; Sponsor: Pfizer; Period of Grant: 2005-2007; Value of Grant: £199,599
- Grant No: RG44738 MAAG/411; PI: Prof W Jones; Grant Title: Preparative methods for co-crystal screen development; Sponsor: Pfizer; Period of Grant: 2006-2009; Value of Grant: £103,100
- Grant No: RG36191 MAAG/163; PI: Prof W Jones; Grant Title: Excipient co-crystals; Sponsor: Pfizer; Period of Grant: 2002-2006; Value of Grant: £66,600
- Grant No: RG36191 MAAG/163; PI: Prof W Jones; Grant Title: Crystal engineering: salt selection and counter ion motifs; Sponsor: Pfizer; Period of Grant: 2002-2005; Value of Grant: £186,975

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

The LAG method developed by the Jones Group is routinely used by industry to search for new solid forms; in particular with regard to poorly soluble drugs, which will have limited bioavailability. The approach allows a complete search of the phase diagram associated with the formation of new solid forms. In addition, intellectual property can exist for each new solid form entity. When searching for new forms drug companies want to be able to screen for all possible forms and develop that form which has the best physical or chemical attributes. By means of this LAG

approach the phase space can be more efficiently explored, in a shorter time scale, with smaller amounts of material (important in early stages of development when sample quantities are small). As a result candidates, which might not otherwise be suitable for commercialisation, can be developed into effective solid forms for formulation into drug products. LAG significantly impacts on how the pharmaceutical industry is able to screen for and discover new solid drug forms.

A number of pharmaceutical companies are known to currently use LAG as part of their drug development process, as evidenced by 3 corroborating statements provided by Amgen, Eli Lilly and Renova Research, and patents that cite the methodology. Further names of companies that can be approached to corroborate that they use the technique are listed in Section 5 and include Pfizer and Vertex Pharmaceuticals.

Quote from Senior Research Advisor, Eli Lilly corroborating letter: "*(W)e have successfully leveraged LAG in recent years to discover new, metastable crystal forms, many of which evaded solution-state crystallization screening…(I)t has been your work around adding small (catalytic) amounts of solvent that has paved the way for us to access more highly crystalline and phase pure crystal forms in high yield. In fact, as a result of your contributions, I am pleased to confirm that LAG has now been incorporated into our solid form screening strategy for enabling forms.*" LC1

Quote from President and CSO, Renova Research, Atlanta, USA, corroborating letter: *"Through my direct interactions and collaborations with Bill Jones I was able to take advantage of the LAG concept to create high throughput LAG screening equipment that would produce 96 experiments in a parallel reaction process. The assistance of the Jones lab was essential to the success of this effort to produce a screening platform that could be used in a production contract research environment."* LC2

A search of US Issued patents referring to methods for co-crystallisation reveals a number of patents that reference the use of LAG and the Jones Group in their methodology indicating that the technique has been adopted across a number of Pharmaceutical industries.

1. US7927613 Filed Sept 2003; Issued April 2011; Assignee: TransForm Pharmaceuticals, Inc. acquired by Johnson & Johnson
2. US7790905 Filed Dec 2003; Issued Sept 2010; & US8183290 Filed July 10; Issued May 2012; Assignee: McNEIL-PPC, Inc.
3. US8241371 Filed Feb 2008; Issued August 2012; & US8241371 Filed Feb 2007; Issued Aug 2012; Assignee: Thar Pharmaceuticals
4. US8212079 Filed Sept 2008; Issued July 2012; Assignee: Aptuit LLC Pharmaceuticals

Some of the reasons LAG has been so readily adopted by the pharmaceutical industry are listed below:

1. Drugs, which might otherwise fail because of property issues (e.g. poor solubility), can be saved by the development of new solid forms and the LAG method allows rapid screening of a range of potential molecules to cocrystallise with the drug (the screening step).
2. The time needed to produce a crystalline form of the drug suitable for large-scale manufacture is significantly reduced. With typical drug sale revenues of the top 10 major drug products each being between 6 and 13 billion US$ per annum, a six month increased revenue can be significant for profits and therefore further support of R & D in other disease areas.
3. Approval of the solid form by regulators (e.g. FDA) can be accelerated by evidence that the proposed marketed form is robust and that a full screening has been undertaken.
4. Small amounts of material are required: In initial stages of drug discovery only small amounts of material are available. The amounts needed for LAG experiments are small – of the order of milligrams, representing a significant cost savings.
5. There is no need to use large amounts of solvent typical of a solution screening approach – with such solvents then being incinerated. This cuts down on waste and lost revenue.

Evidence of some of the advantages of using LAG, and how LAG has resulted in economic impacts such as improved business operations, competitiveness and profitability of industry; as well as environmental impacts through reductions in solvent and consumable waste streams are

available in the letters of corroboration, with selected quotes listed below:

Quote from Preclinical Director, Amgen, Cambridge MA, U.S.A, corroborating letter: *"(T)his reduction in the number of experiments has led to tremendous efficiencies in terms of the amount of compound required, solvent and consumables waste streams, data organization efforts and time required to conduct and complete experiments."* LC3

Quotes from President and CSO, Renova Research, Atlanta, USA, corroborating letter: "*The High Throughput (HT) LAG equipment has had a significant and positive impact on my business operations. To date I have used the HT-LAG equipment to produce 16,128 samples (based on the number of samples logged into the database used to track screening processes). The time savings compared to performing individual reactions is enormous. The 'hands on' time required to do 16,128 reactions individually would be approximately 8064 hours, while the number of hours actually spent creating and analyzing these samples using the HT-LAG approach was only 1680 hours.*

"*Without the HT-LAG system the core operational efficiency required to profitably operate Renovo Research would simply not exist. The LAG screening process constitutes about half of the sample output in a typical commercial screening project, thus a significant portion of the contract research income to Renovo is directly dependent on this technology. The demonstrated ability to perform rapid and comprehensive cocrystal screening was instrumental in the acquisition of $500k USD in investment by a commercial group that contracted with Renovo to rapidly identify cocrystals of key pharmaceutical ingredients that were approaching the end of the patent protected lifecycle. Without the HT-LAG system, Renovo would not have been awarded this contract and could not have completed it within the aggressive time period required by the investors.*"LC2

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

Letters of corroboration available for audit

LC1 Senior Research Advisor, Lilly Research Laboratories, Indianapolis, Indiana, U.S.A
LC2 President and Chief Scientific Officer, Renovo Research, Atlanta, Georgia, U.S.A
LC3 Preclinical Director, Amgen Inc, Cambridge, Massachusetts, U.S.A

Users/Beneficiaries who can be contacted to corroborate claims

1. Head of Materials Sciences in Drug Product Design, Pfizer, UK
2. Senior Director, Vertex Pharmaceuticals Inc, Cambridge, Massachusetts, U.S.A