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Ionic Liquids: A novel green approach to the development of anti-inflammatory drugs

Introduction & Background:

Therapeutic agents are the active components of our medicines and many are not fully effective in patients because of their poor solubility in the gastrointestinal tract. When consumed therefore, such agents are unable to reach their destination sites and are regarded as not being "bioavailable". Considering that many of our modern drugs suffer from inadequate solubility, there is a definite need for smart medicine approaches to make those drugs more bioavailable, but also to ensure that the methods used for producing them are sustainable and environmentally friendly. At present, sustainable practices are not widespread in marketed medicines, as many active agents undergo complex modifications commonly involving solvents that may be toxic to humans and pollute the environment. Development of new approaches to replace those commonly used in the drug manufacturing process is being driven by growing global environmental awareness and by numerous pollution scandals that have resulted in harmful consequences for public health and natural ecosystems [1, 2, 3].

One novel approach to increase the efficacy of poorly soluble drug molecules is to combine them with another harmless compound (the excipient), in a solvent-free, environmentally friendly manner. Combinations used to improve solubility in this way, are called ionic liquids and occur when a solid substance (the poorly soluble drug) interacts with the solid excipient, to spontaneously form a sticky liquid. The drug in this liquid form becomes more soluble and consequently gains increased freedom to move into the bloodstream. This method of improving bioavailability (thereby reducing the dose) is a sustainable approach to increasing the performance of pharmaceutical compounds while simultaneously reducing their environmental impact.

I will specifically work with anti-inflammatory molecules, which are used to reduce swelling and relieve pain. Using this approach, I hope to improve the efficiency of these medications, and ionic liquids in particular are very suited for these purposes. Preliminary screening of literature on pharmaceutical ionic liquids shows that this research it is still in infancy, however it has a unique potential to solve issues associated with poor drug bioavailability and the increasingly serious risk of pharmaceutical pollution. Ionic liquids featured in Nature, where their extraordinary potential for improving drug development, delivery and efficacy was described [4].

Aims & Objectives:

The overall aim of this project is to create novel formulation approaches to aid drug dosage reduction and mitigate the influence of the pharmaceutical industry on the environment. The main objectives of my work will be to:

- Formulate optimal drug/excipient combinations into ionic liquids.
- Analyse product properties and purity.
- Manufacture and characterise my product in tablet form.
- Assess solubility and compare my product using an artificial in vitro model system.

Impact of Research:

One of my main goals is to achieve increased drug bioavailability using ionic liquids thereby reducing the quantities of active agent necessary for therapeutic efficacy. Furthermore, this project will contribute to the "greening" of pharmaceutical manufacturing processes at the research level through formulation, analysis and systematic documentation of innovative experimental procedures undertaken. In this way it will build awareness of alternate, more environmentally friendly practises for the chemical/pharmaceutical community.

Methodology:

My project involves a laboratory-based, hands-on approach to convert active molecules into ionic liquids thereby improving their solubility. I will be the leader of my project and will collaborate with others to achieve my objectives. However, I will be working closely with Dr. Lidia Tajber and will also be strongly supported by her research group, especially when learning new analytical techniques. The schedule of my research is presented below:

- Week 1 – My goal is to review the relevant literature, complete laboratory health and safety training. I will also learn how to use the core techniques of thermal analysis and powder X-ray diffraction to characterise my molecules and confirm their conversion to an ionic liquid.
- Week 2 – I will combine my active molecules with excipients in a solvent-free, sustainable process known as mechanosynthesis using a mortar and pestle and/or a ball mill. Following the synthesis, I will characterise my ionic liquids as in Week 1.
- Week 3 - This week is devoted to analysing results from previous weeks and selecting the most promising for further synthesis. Infrared spectroscopy will be used to verify my products are of a truly ionic nature and I will prepare all components for next week's tableting studies.
- Week 4 – Tablet manufacture and characterisation using methods applied by the pharmaceutical industry in order to establish their performance in "real world" medicine.
- Week 5 – Comparison of my tablets with the traditional marketed product using dissolution, which is an in vitro model to mimic what happens with tablets in the body.
- Week 6 – This will be devoted to discussing all results and drawing my conclusion and recommendations for further studies. Outcomes of my research will be presented, and my personal experiences will be shared at a wider group meeting.

All instruments, and other components needed to carry out my project are available in my supervisor's laboratory, in the School of Pharmacy and Pharmaceutical Sciences. I will have a full access to these, despite the pandemic. My supervisor will ensure that I participate in all weekly group meetings as well as online webinars of her collaborators: COST Action "Mechanochemistry for Sustainable Industry" and events organised by the Synthesis and Solid State Pharmaceutical Centre, offering flexibility in relation COVID19 restrictions. My supervisor will provide me with guidance on research ethics, open scholarship and intellectual property and will explain how to transform my data into a research paper. While I appreciate that 6 weeks is quite short to generate data for a full paper, I hope to be able to partially contribute to a peer-reviewed publication.

References:

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3. Hyderabad's pharmaceutical and pollution crisis: heavy metal and solvent contamination at factories In a major Indian manufacturing hub. (Jan, 2018) Nordea and the changing markets foundation.
4. Shamshina, JL, Kelley, SP, Gurau, G & Rogers, RD 2015, 'Chemistry: Develop ionic liquid drugs', Nature, vol. 528, no. 7581, pp. 188–189