IMPACT

WORKING TOWARDS A GREENER PHARMACEUTICAL INDUSTRY

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FACULDADE DE CIÊNCIAS E TECNOLOGIA UNIVERSIDADE NOVA DE LISBOA

LAQV

FCT Fundação para a Ciência e a Tecnologia

Impact Objectives

- Design a solvent-free and sustainable process for the enzymatic separation of enantiomers
- Gain a greater understanding of the properties and behaviour of deep eutectic solvents (DES), so as to be able to design and characterise new DES and to develop new applications
- Continue to delve deeper into the therapeutic applications of eutectic solvents (THEDES), particularly in relation to the potential offered in the field of drug delivery

Working towards a greener pharmaceutical industry

There is an increasing emphasis within the chemical industry to embrace and emphasise so-called green and natural chemicals in everyday processes and reduce the overall burden on the planet. ***Dr Alexandre Paiva*** *is investigating the use of deep eutectic solvents in this field*

Could you explain the key objectives of your project 'Biocatalytic separation of enantiomers using Natural Deep Eutectic Solvents (DESZyme)'?

The main goal of the project is to design a completely sustainable process for the separation of enantiomers of sec-alcohols with interest for the pharmaceutical industry. The enzymatic separation of enantiomers is a greener alternative to the highly intensive chemical processes that produce high amounts of waste. However, for the enzymatic process to be viable, it is necessary to use organic solvents. The goal of DESZyme is thus to design a solvent-free process for the enzymatic separation of enantiomers, designing a completely sustainable process.

As deep eutectic solvents (DES) are a new class of solvents, there is still much to understand about their properties and behaviour. Therefore, it is also the objective of DESZyme to design and characterise new DES and to develop new applications for these solvents.

Can you expand on what Natural Deep Eutectic Solvents (NADES) are?

NADES were hypothesised as an alternative medium that are present in living cells, composed by metabolites that are present in organisms in large quantities such as sugars, amino acids, organic acids or choline. The hypothesis is that these metabolites form a third type of cellular liquid, different from aqueous and lipidic media, where species of intermediate polarities are dissolved and can be transported within the cell. When it was observed that combinations of these metabolites can behave as eutectic mixtures or solvents, the hypothesis of NADES gained strength. NADES can be formed for example, mixing sucrose and citric acid, sucrose and fructose or even choline chloride and citric acid, among many other compounds.

The combination of NADES and supercritical carbon dioxide can be envisaged as an integrated process, where we use two green solvents. NADES are envisaged as having low solubility in supercritical carbon dioxide, although they present good values for carbon dioxide solubility. Taking this into account, processes such as extraction, polymer processing and stabilisation of extracts have already been carried out and can be further planned.

What results have you garnered so far?

Since the start of the DESZyme project, we have been able to prove the use of more common DES, for example composed of choline chloride and urea, as solvents for biocatalytic processes. This is very interesting since DES are generally regarded as non-toxic and safe solvents, meaning we circumvent the volatile organic compound emissions, and the downstream purification processing of the reaction products is much simpler or even non-existent.

Moreover, we have been able to obtain satisfactory results using DES, not only as biocatalytic reaction media, but also as a source of reactants. We are now evaluating all the factors that affect the reaction and enzyme, and also the alterations in the DES that occur during the reaction. This strategy is proving successful and when all the reaction parameters are optimised, depending on the DES of course, it is going to be a simple, fast and cost-effective method to carry out biocatalysed reactions.

What are the real-world applications for your work?

The real-world applications of DESZyme will benefit mainly the biomedical and pharmaceutical industries. Naturally, by designing greener processes for the development of enantiomeric pure components, thus substituting the current ones, there is also a clear benefit for the environment and society. The therapeutic applications of eutectic solvents (THEDES) also improve the bioavailability of active pharmaceutics ingredients (APIs), so there is also a clear benefit for these industries in the development of new, more effective drug delivery systems. ●

Deep eutectic solvents in biocompatible chemical systems

The increasing interest in the use of deep eutectic solvents as a replacement for many, potentially more harmful solvents, has fuelled research into these reagents as convenient media for synthetic chemical routes. ***Dr Alexandre Paiva*** *is at the forefront of research into this exciting field*

Green chemistry is big news. The need to reduce the amount of toxic and hazardous substances in processes has fuelled a growing interest in the use of chemicals, which are both natural and degrade in a safe way, without affecting the environment. The principles cover such concepts as the prevention rather than the cleaning of waste, less hazardous chemical syntheses, the use of renewable feedstocks, and employing safer solvents and auxiliaries.

Green chemistry encompasses the design of processes to maximize the amount of raw material that ends up in the product and includes four basic tenets. These are: the use of renewable material feedstocks and energy sources; the use of safe and environmentally benign substances; and the design of energy efficient processes, which avoid waste. While there are many areas of chemistry where this ethos is still in its infancy, it is becoming well understood in the specialised field of solvents. The chemical industry consumes solvents in large quantities in many chemical syntheses, as well as ancillary operations such as cleaning and degreasing, and traditional solvents are often either toxic or chlorinated. Green solvents, on the other hand, are generally derived from renewable resources and biodegrade in nature. The most exciting of these are termed deep eutectic solvents and are the current research focus of Dr Alexandre Paiva.

OFFERING SIMPLE SOLUTIONS

Deep eutectic solvents are systems typically formed from a mixture of hydrogen bond donors and acceptors, which can contain a variety of anionic and/or cationic species. Critically, these solvents are regarded as being green and have little impact on the environment, and that makes them especially interesting to many areas of the chemical industry. Natural deep eutectic solvents (NADES) were first understood as a medium present in living cells and are different from both the usual aqueous and lipid media. When it was established that different combinations of these metabolites were in fact a driving force in cellular activity, it was also observed that they were effectively eutectic solvents. The theory behind NADES was developed and they have since become a major tool in green chemistry, particularly in the processing of biopolymers.

NADES are hugely advantageous because of their natural low toxicity, biodegradability, and the fact they are biocompatible with many media. Furthermore, they have negligible vapour pressure, so do not succumb to problems with emissions during processing, making them an ideal solvent. While NADES usually need to be assessed for toxicity in specific applications, these are usually unlikely, making them highly desirable in many applications. However, development of deep eutectic solvents has extended beyond even the concept of NADES and their use in therapeutic applications is being actively pursued. Termed THEDES, the therapeutic possibilities of eutectic solvents are an area of great interest, as they have the potential to offer drug delivery with few, if any, harmful aspects.

DEVELOPING DEEP EUTECTIC SOLVENTS

While the possibilities of what deep eutectic solvents in all their forms may be able to offer are still being investigated and evaluated, Paiva is likely to be at the forefront of research. Having completed a degree working with supercritical fluids, he became interested in the concept of green and sustainable chemistry and it was through this interest that he first encountered deep eutectic solvents. Starting from the basics of a compound of two solid components that experience a phase change and melt at a lower than expected temperature, Paiva combined this with knowledge on enzymes and green solvents and developed the DESZyme project.

Paiva describes the main goals of the project as the design of a process aimed at the separation of enantiomers – optical isomers that represent mirror images of each other, such as D-glucose and L-glucose – of sec-alcohols for the pharmaceutical industry. The current process tends to be highly intensive and generates a high volume of waste product, so the industry was keen to turn to an alternative with established green chemistry credentials. Paiva's project looks to establish the use of a process that doesn't need to use the usual organic solvents, but could still be used for the effective separation of enantiomers and remain a sustainable method. ▶

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The process has been shown to be both effective and suitably clean for the industry, though there is still much that needs to be understood about the properties and behaviour in the process of the eutectic solvents, and this is now the main thrust of the project. With the potential for many other processes to benefit from these new compounds, Paiva is investigating further uses for this exciting area of chemistry. That fact alone has driven research into NADES.

SOLVENTS OF THE FUTURE?

Following the successful work with enantiomer separation, Paiva has turned his attention to the possibility of NADES as routine solvents within many chemically-driven industries. The research has so far determined they can be used as extraction solvents and have been shown to be increasingly effective when used together with supercritical carbon dioxide to create a fast and safe solvent system in polymer engineering. But this is a fast-moving project and research has already turned to the potential of THEDES, and this has become the main area of interest for Paiva. He has so far been able to form them with several different therapeutic compounds and has created liquid forms at room temperature.

However, much of this work has been completed through trial and error, rather than by fully understanding the processes involved, and work is now being carried out using both spectroscopic and computational techniques to add further dimensions to the investigation. This has now become the main area of research for the investigation, as the team start to gather data to explain the interactions that result in deep eutectic solvents presenting enhanced solubility and bioavailability when in the THEDES form. This is an expanding field of research and the potential uses of DES and THEDES are growing at an exponential rate.

TAKING IT FORWARD

The current project integrates a good deal of fundamental research into the nature of deep eutectic solvents, along with the natural and therapeutic variants of them. Paiva sees this being carried out as a set of different work packages that will advance our understanding of these exciting new systems. Primarily, the team are working on the development of new DES and NADES systems, while simultaneously carrying out characterising them. As this work continues, the team will also study the process of enzymatic esterification, while another work package will focus on the phase behaviour of DES with supercritical carbon dioxide.

The project has taken the concept of deep eutectic solvents from first principles and grown to expand both the usability and the potential for them in the context of green chemistry. The biomedical and pharmaceutical industries are most likely to benefit from the use of deep eutectic solvents and are collaborating with Paiva and his team to push the use of these materials and their derivatives forward. The results of this are likely to have a profound impact on an industry that desires effective processes, but must ensure they make the least impact possible on the environment. Deep eutectic solvents, along with NADES and THEDES, have the potential to fulfil both of those criteria. ●

Project Insights

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PROJECT COORDINATOR BIO
Alexandre Paiva obtained his PhD in Chemical Engineering – Thermodynamics and Biocatalysis – from TUHH in 2008. From 2008-16 he was a Post-doc researcher at FCT-NOVA, Portugal. Since 2016, he has been a senior researcher and assistant lecturer at LAQV/FCT-NOVA. His main areas of expertise are sub-, supercritical fluids, biocatalysis and deep eutectic solvents.

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