Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

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Charles Institute of Dermatology

Topical issues in dermatology

Attendees at UCD's Charles Institute Seminar Series heard a presentation on the challenges faced by healthcare professionals in delivering topical therapies to patients in an effective way

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert practical advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. Each seminar in the series was broadcast to attendees with a special interest in dermatology in other locations, who accessed each talk remotely via an audio-visual link.

Attendees at the seminar series heard a presentation from Dr Majella E Lane, who is a consultant for a number of cosmetic and pharmaceutical companies and is Editor-in-Chief of the International Journal of Cosmetic Science, as well as serving on the boards of several pharmaceutical and cosmetic science journals. Dr Lane earned her BSc in Pharmaceutical Science and PhD in membrane transport at Trinity College Dublin and heads a research group that collaborates globally and hosts visiting scientists from academia and industry to help raise awareness and education of the mechanisms of topical formulations.

Dr Lane delivered a presentation titled 'Skin Health and the Importance of Topical Formulation Design' and explained to attendees the difficulties in targeting active therapies to specific regions of the dermis and epidermis, as skin penetration with most 'actives' (active ingredients) often does not exceed more than 2-to-4 per cent of the amount that is applied. She also referenced a study involving hydrocortisone. "Hydrocortisone is actually not that difficult to deliver to the skin," said Dr Lane, "but this study shows that only 1 per cent of the initial dose that was applied ended up in the [patient's] urine — and that means that less than 2 per cent was actually absorbed through the skin."

A calculation could be extrapolated from this finding, Dr Lane continued. "So if you were to apply hydrocortisone all over the body, the maximum amount absorbed would be 4 milligrams," she told the seminar. "So, using that example, it is clear that those of us who work in delivering therapies through the skin are working in a challenging environment."

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Evaporation

Another problem arises when a cream or gel is applied to the skin, said Dr Lane, as very quickly, there will be evaporation and there will also be a number of solvents in any topical preparation. "Remember, we can only get the active of the drug into the skin lipids and yet by volume, they only occupy 20 per cent of the outer layers of the skin," she explained. "That means that it is quite easy to overload the lipids, and when you do that, the drug comes out of solution and crystallises."

Another problem is posed by the fact that creams are emulsions so what begins as an oil and water emulsion often just ends up as oil on the skin, Dr Lane explained. "You really do need to understand the composition of that residual phase on the skin," said Dr Lane. "And of course, sometimes patients don't help if they don't apply the product properly, so all of that adds to the challenges in this area."

Dr Lane presented research involving ethanol, showing that while some formulations enter the skin, they often do not reach their target. "Think of the stratum corneum as bricks, and then you have the lipid," she explained. "The ethanol is 'crashing' the drug largely on the surface of the skin. A solvent such as dimethyl sulphoxide is taking the active into the skin but eventually, the active crashes in the skin too because the DSMO is moving, but the drug itself is not. So a lot of your formulation is wasted if you do not think carefully about what is in it."

Penetration enhancers

Dr Lane also provided an overview of an area in which she has been involved for some years — skin penetration enhancers. "The right skin penetration enhancers limit the problem of drug crystallisation," she said. "Essentially, they help the drug move into the skin and move through the skin by interacting with the stratum corneum. We don't know for certain yet what the exact mechanisms of action of these skin penetration enhancers are, but we believe there is interaction between these compounds with parts of the lipids themselves, and perhaps some cases, some separate phase formation of the enhancers in the skin.

"If you pick more than one enhancer you may get synergy, and that will also help to push a drug into the skin."

Dr Lane explained that there are penetration enhancers in most formulations, even in cosmetics. "What you are looking for in these enhancers are long-chain fatty acids, esters of fatty acids, alcohols or glycols," she told the seminar. "Chemically, they are quite diverse — we want to use simple enhancers, but also enhancers that have different mechanisms of action. We think that these compounds work by pushing the drug in, or by increasing the ability of the drug to move into the skin, or by increasing the residence time of the drug in the stratum corneum."

Dr Lane explained that much research has been dedicated to studying topical drug therapies through the years, but far less attention has been focused on the actual delivery vehicle for the drug to ensure its efficacy. "It's quite a simple concept," she said. "The fate of the excipients in the vehicle is linked to the fate of the active. If you don't know the residence time of the excipient, you can't be confident that the drug has reached its target. It's important to consider what is left on the skin when the patient has applied it properly, and then you can design the enhancing technology into that residual phase. So that's the question you need to ask from the beginning — where is it you want the drug to go to, and how will you create a formulation which has that correct driving force?"

She told the attendees about new approaches designed to measure how much of a given drug actually penetrates the skin. These include tape-stripping and microdialysis, while some drugs have pharmacodynamic end-points, such as steroids. "For some drugs, we have no option but to take pharmacokinetic measurements — one example would be the lidocaine patch for post-herpetic neuralgia.

"The technique that I have been working on for the past few years is confocal Raman spectroscopy," said Dr Lane, while presenting brief overviews of each method. "Tape-stripping has been of interest to skin specialists for a long time. Essentially, it involves application of the formulation to a defined skin area, uniform distribution of the product; you then apply an adhesive with a fixed amount of pressure, and you strip off the adhesive tape and measure what is left on the tape. I have never considered it the most elegant method, but it was the focus of a lot of US FDA funding for a lot of years," said Dr Lane. "That was as good as we had for a long time… but the tape-stripping process cannot tell you whether the drug is in solution or whether it has crashed-out."

To obtain a profile of the amount of drug in the skin over a period of time, Raman spectroscopy uses a vibration spectroscopy technique; excitation of the molecules results in scattered radiation, which can reveal not only the drug movement within the skin, but information about the skin itself, said Dr Lane. "It is a non-invasive technique… with high spatial resolution and it has been tested extensively," she explained. "There are no dyes or labels required and it can give you a lot of information about the stratum corneum, but also about some of the deeper layers."

Dr Lane summarised her presentation by telling attendees and those listening to her talk remotely: "The newer analytical methods are really powerful in helping us to establish if formulations are doing what they are supposed to be doing and in helping us to understand where they are actually going

Dr Majella E Lane

in the skin," she said. "But we still need to have a better understanding of how what you get into the outer layers correlates with the deeper layers of skin.

"There should be a simple flow from the barrier — simple diffusion — but that's not what we are seeing. Also, we should not ignore the vehicle components; it's not difficult to read a label and identify what might be a penetration enhancer… people should talk to their pharmacist, as they are the experts in formulations," she concluded.

Water solubility

During a lively interactive Q&A session, Prof Tobin raised the point of penetration enhancers and whether these actually physically chemically bind to a drug. This is important in the context of whether penetration enhancers go with a drug, go ahead of it or are transported behind it, added Prof Tobin. Dr Lane responded: "The way penetration enhancers work is generally by acting simply as a vehicle. Many of the drugs we put on the skin are not very water-soluble and to make a formulation, we need it to have some degree of water-solubility," she explained.

"Simply put, the penetration enhancer changes the 'identity' of the active by keeping it in solution and a penetration enhancer makes the skin a more suitable environment for a drug, so it transiently changes the solubility of both the skin and the active — it bridges the difference in the solubility of both."

Speaking with the ***Medical Independent*** (***MI***) following her presentation, Dr Lane commented on the need for more awareness of and research into the mechanisms of delivery for actives used in a range of dermatological conditions. "It's important to remember that dermatology is the 'Cinderella' of pharmaceuticals," she said. "Most drugs are administered via the oral route, so there has been a lot more research and Government funding put into that, and one could argue that this is the right area to spend this money and time on.

"On the other hand, we all put things on our skin every day, even if it is just moisturisers," she told ***MI***. "So it seems to me that there needs to be more attention focused on topical preparations, whether these are simple moisturisers, or skin creams and ointments. I think we need to look at the curricula for GPs and pharmacists — and nurses too — and bring people together to try to increase our knowledge of skin products and therapies and how to choose the best ones for a patient or consumer. The skin is our barrier — it keeps us alive in a dry world and we need to take care of it," she concluded.

RELIFE has had no input into the content of this article or series of seminars.