AQUARMED™: TRANSDERMAL DELIVERY USING NOVEL COMPONENTS DERIVED FROM NATURAL MOISTURISING FACTOR (NMF)

In the following article, Professor Marc Brown, Chief Scientific Officer; Professor Adrian Williams, Member of Scientific Advisory Board; and James Gibbons, Commercial Manager, all of MedPharm, explain how the company has developed AquaRMed, a series of rationally designed hydrotopes that increase hydration of the skin, show anti pro-inflammatory properties and are proven penetration enhancers for topically and transdermally delivered APIs, and describe the potential benefits AquaRMed could offer patients and companies alike.

INTRODUCTION

The transdermal and topical drug delivery market is expected to reach a size of US$31.5 billion (£21.4 billion) this year.[1] This is largely the result of companies increasingly looking to take advantage of the benefits of delivering therapeutics via these routes. Such advantages range from avoidance of first-pass metabolism, to enhanced patient compliance, to product lifecycle management and brand line extension.

MedPharm, the leading topical and transdermal formulation development, testing and clinical supplies manufacturing company, helps its clients develop products for this market. As part of its continuing push for innovation MedPharm has developed an exciting, novel skin hydration technology called AquaRMed™. The technology shows promise as a new topical and transdermal drug delivery technology.

AquaRMed is a series of rationally designed hydrotopes that increase hydration of the skin, show anti pro-inflammatory properties, and are proven penetration enhancers for topically and transdermally delivered active pharmaceutical ingredients (APIs). MedPharm has patented these hydrotopes and is continuing to evaluate the technology with a view to commercialisation through collaborations with its licensees.

BACKGROUND

MedPharm has extensive expertise in developing topical and transdermal medications and has contributed to the development of more than 20 marketed products in its 16-year history. With this expertise, MedPharm has continuously strived to find the newest and best innovations to help its clients develop successful, safe and efficacious products; these include proprietary efficacy testing models and drug delivery technologies.

MedPharm's latest innovation, AquaRMed consists of a series of hydrotopes adapted from Natural Moisturising Factor (NMF), which comprises a number of compounds including urea, peptides, amino acids, sugars, lactates, inorganic acids and a variety of salts that aid water retention within the *stratum corneum* in normal physiology.[2]

NMF itself is a hydrolysis product of filaggrin, and dry, inflammatory skin conditions such as atopic dermatitis are linked to a decrease in NMF. Patients often have fewer filaggrin repeat units in the FLG gene and patients with ichthyosis vulgaris have loss of function mutations in filaggrin genes. These changes lead to a decrease in filaggrin produced and consequently a decrease in NMF levels.[3] In addition, atopic dermatitis patients with filaggrin gene mutations resulting in decreased NMF inversely show an increase in the *stratum corneum* concentration of pro-

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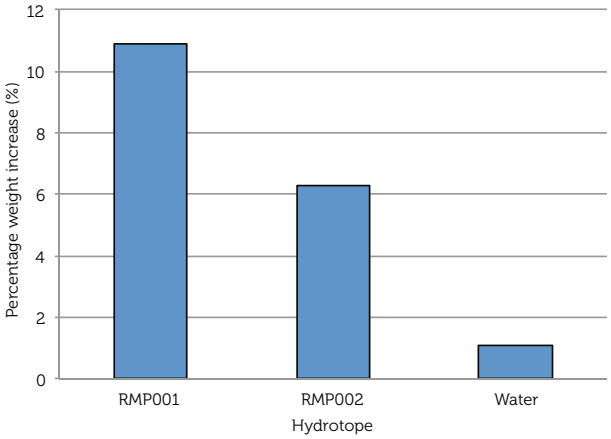

Figure 1: Weight gain of snake skin treated with AquaRMed (RMP001 and RMP002) and stored at 40% room humidity as an indication of hydration.

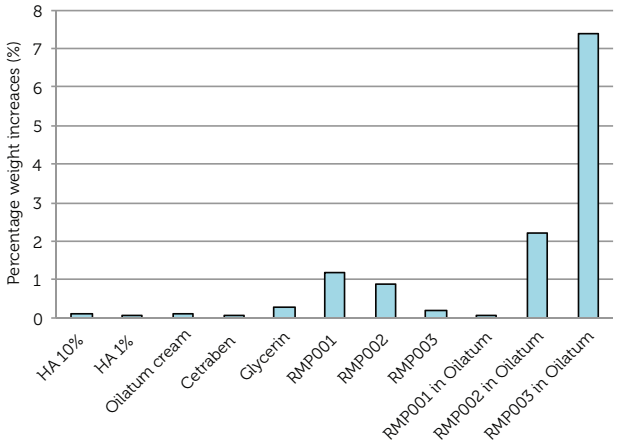

Figure 2: Weight gain as an indication of hydration following application of AquaRMed molecules (RMPXXX) and marketed moisturisers, in combination and separately (Snake skin).

inflammatory cytokine IL-1.[4] Therefore, topically applied NMF replacement has potential therapeutic benefit. With this rationale, Professors Brown and Williams aimed to develop a series of compounds that they hoped could be used to treat xerotic and inflammatory skin conditions.

AQUARMED DEVELOPMENT & EVALUATION

MedPharm developed methods to synthesise a series of compounds derived from NMF which, when left at normal room humidity, deliquesce by absorption of atmospheric water. MedPharm has now conducted a number of studies showing increased skin hydration in an *in vitro* and *ex vivo* setting. *Ex vivo* snake skin was initially used to show hydration was improved by AquaRMed molecules. Chosen because snake skin intrinsically lacks NMF, hydration was quantified by measuring weight gain (Figure 1). A significant increase in skin hydration is seen in the skin treated with AquaRMed, compared with water.

With further evaluation warranted, MedPharm next performed studies to establish hydration performance of AquaRMed compared with marketed products and other known emollients in snake skin (Figure 2), and human epidermis (Figure 3). Two of three AquaRMed hydrotopes (RMP001 and 002) performed better than all marketed moisturisers tested in these assays.

Interesting trends are apparent in Figure 3: when AquaRMed was physically combined with marketed moisturiser, oilatium (GSK), in an un-optimised formulation, there was a marked increase in hydration when compared with the moisturiser and AquaRMed molecules in isolation. However, it is important to consider that these early experiments utilise un-optimised AquaRMed solutions; thus fully optimised formulations of AquaRMed should perform even better in such hydration experiments than the results reported here show.

It is a widely accepted fact that hydration of the *stratum corneum* enhances API delivery into and across the skin, with significant enhancement possible.[5] For this reason, many topical and transdermal formulations are made to be occlusive as they reduce water loss from the skin, consequently increasing skin hydration and, therefore, API delivery. AquaRMed molecules actively hydrate the skin. With this in mind, MedPharm undertook a number of permeation and penetration studies (human epidermal sheet mounted in Franz-cells) to assess the delivery enhancement properties of AquaRMed using three model drugs (Figure 4).

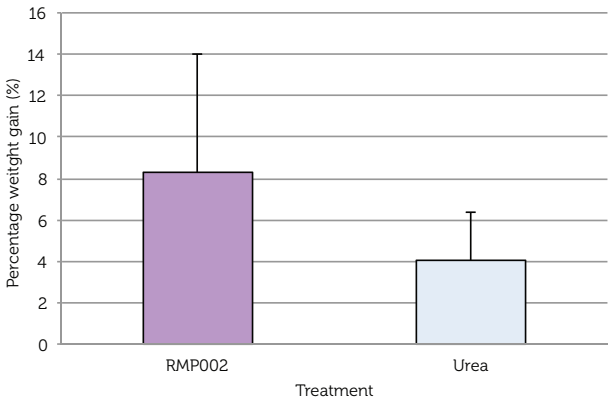

Figure 3: Weight gain of human epidermis as an indication of hydration following application of AquaRMed molecule (RMP002) compared with urea.

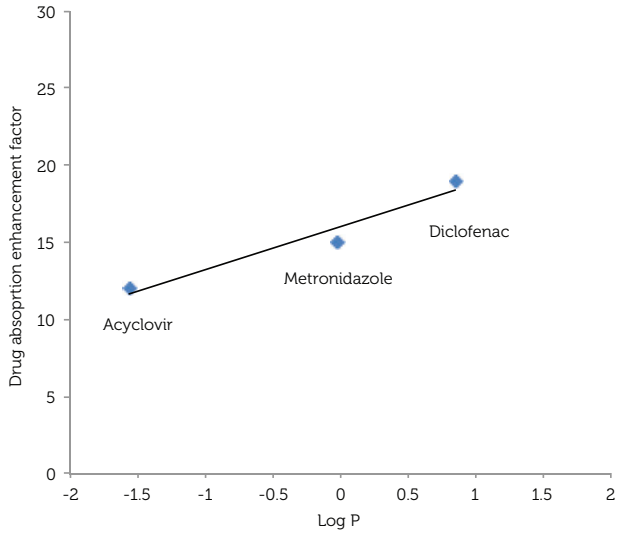

Figure 4: AquaRMed enhancement of API permeation across human epidermal sheet. Tissue pre-treated with AquaRMed or water (control) prior to model drug application; indication of LogP trend.

A significant enhancement of permeation has been observed in these studies, when AquaRMed is applied to the skin prior to the model drug. Up to a 20-fold increase in delivery was observed when diclofenac was administered following pretreatment with AquaRMed compared to diclofenac application without AquaRMed pre-treatment.

Similar enhancements were seen with metronidazole (circa 14-fold increase in delivery) and acyclovir (circa 11-fold increase in transdermal delivery). It is currently hypothesised by MedPharm that permeation enhancement magnitude correlates with the Log P of the API; i.e. the more lipophilic the drug, the greater the possible delivery enhancement (Figure 4). Further studies are ongoing to assess this theory.

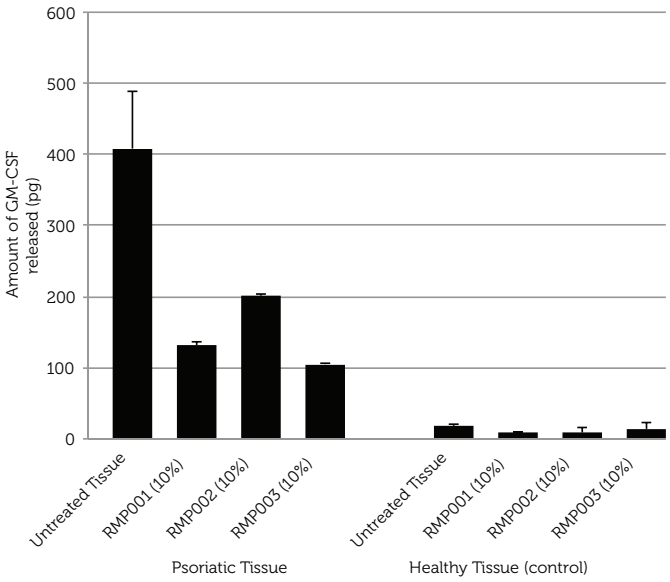

Figure 5: AquaRMed attenuation of GM-CSF release in psoriatic skin model and healthy tissue (RHE) controls.

With AquaRMed's potential as a high performing drug delivery technology validated, it was next important for MedPharm to study the safety of using AquaRMed on human skin. Irritation and toxicity profiles for AquaRMed molecules were expected to reflect their nature as endogenous substance derivatives. Theoretical toxicity reviews conducted by an independent party concluded that there were unlikely to be toxicity issues with the technology.

These theoretical predictions were supported by some *in vitro* tests conducted at MedPharm. Acute skin irritation was assessed using the SkinEthic Skin Irritation Test where AquaRMed molecules were applied to reconstructed human epidermis (RHE) tissues. The RHE tissues were incubated for 24 hours, and then assessed by MTT assay and measurement of cytokine release. ET-50 values (the time at which 50% of cultured cells are no longer viable) were also calculated using MatTek's MTT ET-50 assays. The results of these tests showed that two of the three molecules were non-irritant, with the third comparative to baby shampoo as a very mild irritant.

The advantages of treating xerotic skin conditions with AquaRMed are clear from a hydration point of view. With the hope of extending this therapeutic benefit to inflammatory skin conditions, MedPharm has also assessed the anti-pro-inflammatory properties of AquaRMed. Kezic and co-workers have previously documented NMF's role in the immune response system, showing that IL-1 levels increase in the *stratum corneum* with a decrease in NMF.[4]

MedPharm used a human cell culture based psoriatic tissue model consisting of psoriatic lesion-derived fibroblasts and normal keratinocytes to test AquaRMed's anti pro-inflammatory properties. This *in vitro* model exhibits hyperproliferation of basal epithelial cells and increased expression of pro-inflammatory cytokines and other inflammatory markers associated with psoriasis (e.g. GM-CSF) when compared to normal RHE cultures. GM-CSF is a key activator of the innate immune system involved in chronic inflammatory and autoimmune diseases such as psoriasis,[6] where macrophages, granulocytes, neutrophils, eosinophils and dendritic cells contribute to tissue damage and disease progression.[7] Numerous *in vivo* studies over the past few years have shown that blockade of GM-CSF via neutralising antibodies can prevent or even cure pro-inflammatory diseases in various models of inflammation including psoriasis.[8] In addition, patients with chronic psoriasis receiving GM-CSF therapy have been shown to have exacerbated psoriatic lesions.[9]

Due to the importance of GM-CSF in psoriasis it was selected for quantification in experiments with AquaRMed (Figure 5). A reduction in GM-CSF release was observed when the psoriatic tissue model was treated with three different AquaRMed molecules, suggesting an additional application for the technology in the treatment of inflammatory skin diseases. Indeed, GM-CSF release was halved over the course of six days following AquaRMed application to the cell cultures.

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FUTURE PLANS

MedPharm is continuing to work on these non-toxic moisturising compounds to evaluate their penetration enhancing capabilities further using both a number of its licensees' APIs and additional model drugs, with promising results to date.

A PCT patent was filed in November 2013. MedPharm is evaluating a number of commercialisation strategies, including development of AquaRMed molecules as novel excipients that would offer a safe and elegant way to enhance topical and transdermal drug delivery.

The benefits of using AquaRMed molecules as a delivery technology are numerous; they could offer patent protection to formulations containing AquaRMed as one advantage. AquaRMed also offers notable enhancement in topical and transdermal delivery without the need for use of expensive, and often complex, drug delivery technologies such as microneedles, and active delivery systems such as phonophoresis and electrophoresis.

As part of the commercialisation process MedPharm also is evaluating the possibility of developing a portfolio of products that would include dry and inflamed skin condition treatments. These products would include AquaRMed in combination with APIs. MedPharm is currently conducting several feasibility studies with its licensees'

APIs, and is actively pursuing the possibility of licensing the technology to its clients.

CONCLUSIONS

MedPharm has developed a novel technology that, even at an early stage, offers significantly increased skin hydration when compared with the hydration ability of currently marketed emollients and humectants. In addition, human skin permeation studies have shown the potential for AquaRMed to enhance API delivery to and across the skin significantly.

AquaRMed appears to be non-irritant and may have additional anti pro-inflammatory properties.

Thus, the technology has potential application for the treatment of inflammatory and xerotic skin conditions, providing notable improvements to therapies in a market often dominated by steroid based medicines. There is also significant potential for the use of AquaRMed as a topical and transdermal delivery technology with numerous advantages over other technologies available.

MedPharm welcomes enquiries regarding assessment of AquaRMed's drug delivery potential with a view to finding new licensing partners.

ACKNOWLEDGEMENTS

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