Evaluation of penetration kinetics of commercial topical formulations in human skin using non-invasive confocal Raman microscopy

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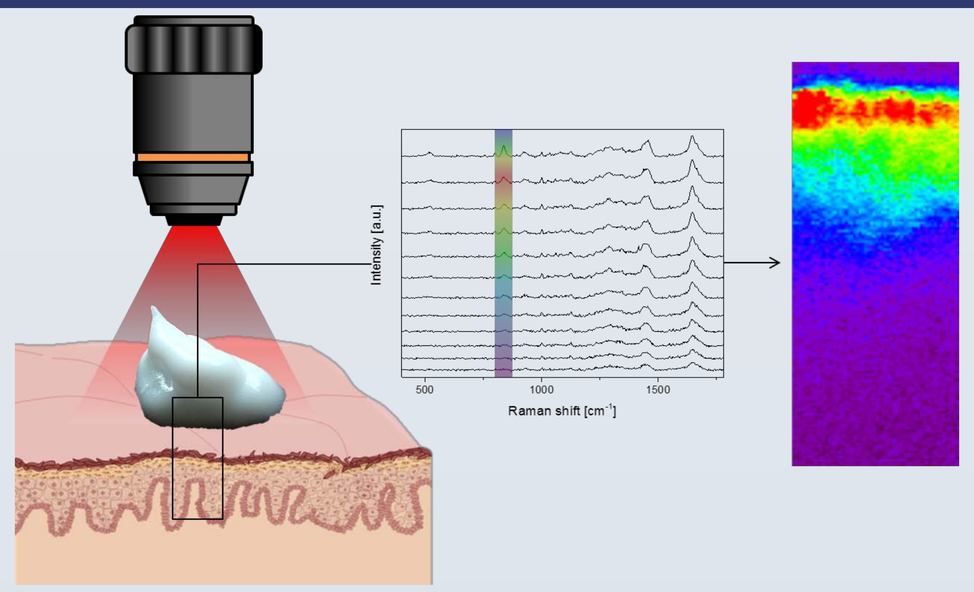
Introduction

The design, manufacture, performance and control of complex topical drug products collectively requires an thorough understanding of the physical and structural characteristics of the semisolid formulation. It also requires an understanding of the interaction of the topical dosage form with human skin. Established techniques often provide limited information on compositional changes occurring within a topical formulation as a result of the interaction with skin tissue. Also, these analytical techniques often fail at combining chemical and spatially resolved compositional analysis, impeding our ability to detect potential microstructural changes within a topical product and the resulting effects of the formulation on the skin, itself.

In this study, chemically selective, confocal Raman microscopy was used for the characterization of commercial topical formulations and their interaction with excised human skin tissue without the need for labels, dyes or destruction of the sample[1,2].



Methodology & Results

Methodology

Six commercial topical 5% acyclovir cream products were characterized regarding compositional arrangement of matter. Also, the influence of mechanical stress (here referred to as "in use conditions") on the products was assessed and penetration kinetics of the creams within full-thickness human skin were observed by monitoring the skin penetration of a formulation component, propylene glycol, over to 24 hours within the upper epidermis. An Alpha300R$^+$ confocal Raman microscope (WITec GmbH, Ulm, Germany) equipped with a 785 nm laser (50 mW) was used to analyse chemical properties of the commercial creams (integration time 0.1 sec, step size 0.5 µm) and their penetration into excised human skin tissue (integration time 30 sec, step size 2.0 µm). Hierarchical cluster and subsequent basis analysis were performed to create false-color images.

Raman analysis of semisolid products

In the investigated commercial products, acyclovir crystals are suspended within a cream base, as depicted by false color Raman images for a U.S. marketed reference cream (A) and an Austrian generic product (B), as shown below. The drug crystals (yellow) as well as the cream base (black) display no significant differences between the two cream products, as shown in the respective Raman spectra below (C). Shape and size of the drug crystals differ between the two products. Comparison of Raman spectra of drug crystals of all six tested products with Raman spectra of different polymorphic forms of acyclovir identified the presence of the polymorphic form V in all formulations (D).

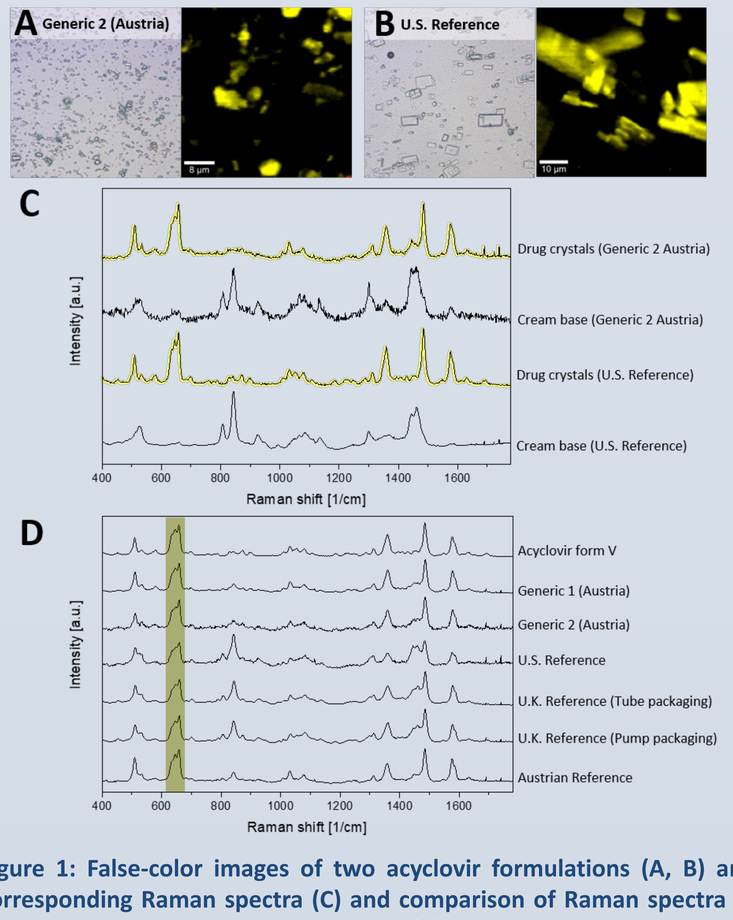


Figure 1: False-color images of two acyclovir formulations (A, B) and corresponding Raman spectra (C) and comparison of Raman spectra of acyclovir in six different cream products (B).

Effect of mechanical stress on microstructure

Light microscopy and Raman scans show that upon application of mechanical stress (pumping) to a U.K. reference cream product, phase separation is observed within the cream base as shown in (B). Raman identified globules to be comprised of dimethicone (C). 3D reconstructions from Raman scans show differences in microstructure between products from tube and pump packaging (D).

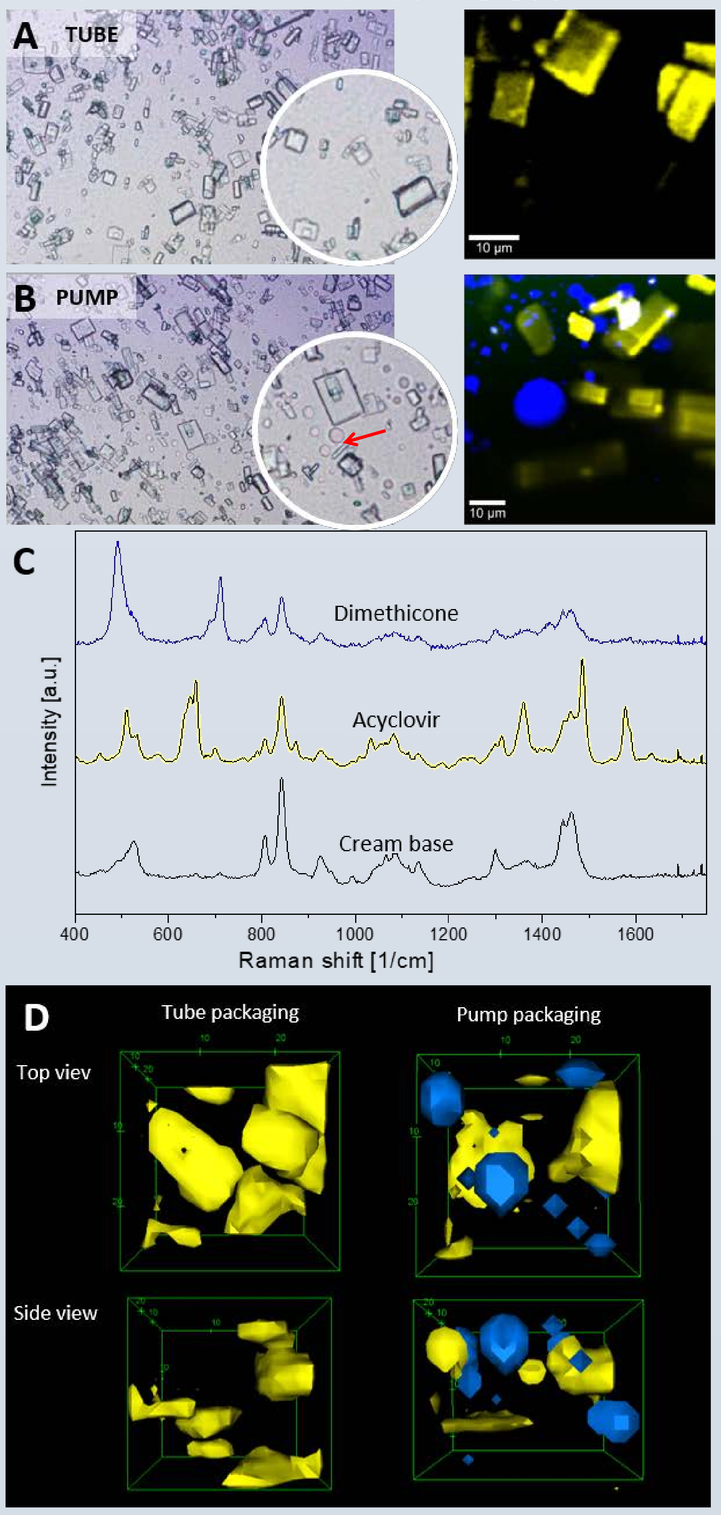


Figure 2: Light microscopy and Raman images of U.K. reference products dispensed from tube (A) and pump containers (B), corresponding Raman spectra (C) and 3D reconstructions of the cream systems (D).

Assessing skin penetration

Raman microscopy was used to generate penetration depth profiles of different cream products within human skin, monitoring propylene glycol (penetration enhancer). A formulation-associated Raman peak was selected (A) and normalized by a skin-derived Raman peak to account for the depth attenuation of the signal (B). The intensity was subsequently plotted against penetration depth (C).

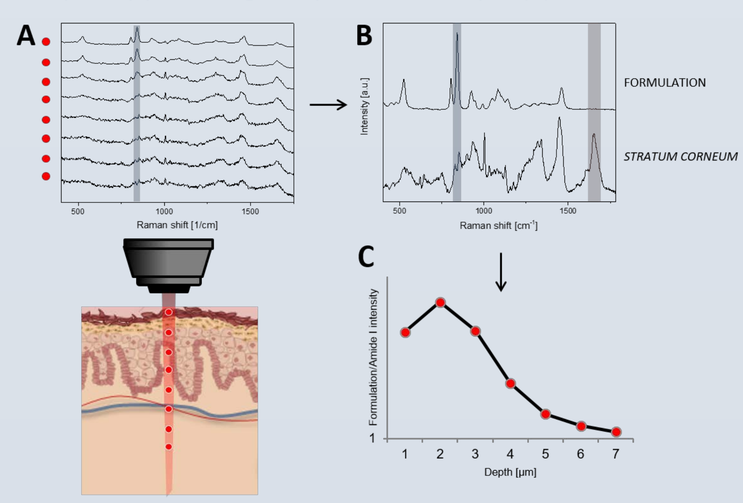


Figure 3: Acquisition of Raman skin penetration profiles.

The penetration profiles of propylene glycol from six commercial acyclovir (ACV) creams (4 reference products, 2 Austrian generic creams) were assessed by Raman microscopy after 4 h and 24 h of incubation on the skin (A). After 4 h, no significant difference could be observed between the products. After 24 h, the U.S. reference cream (red) showed higher Raman intensities of propylene glycol in the upper epidermal layer as well as deeper penetration compared to other reference and generic products (yellow, green). These results of higher propylene glycol penetration correlated with higher acyclovir permeation evaluated by *in vitro* permeation test (IVPT) using Franz diffusion cells (B).

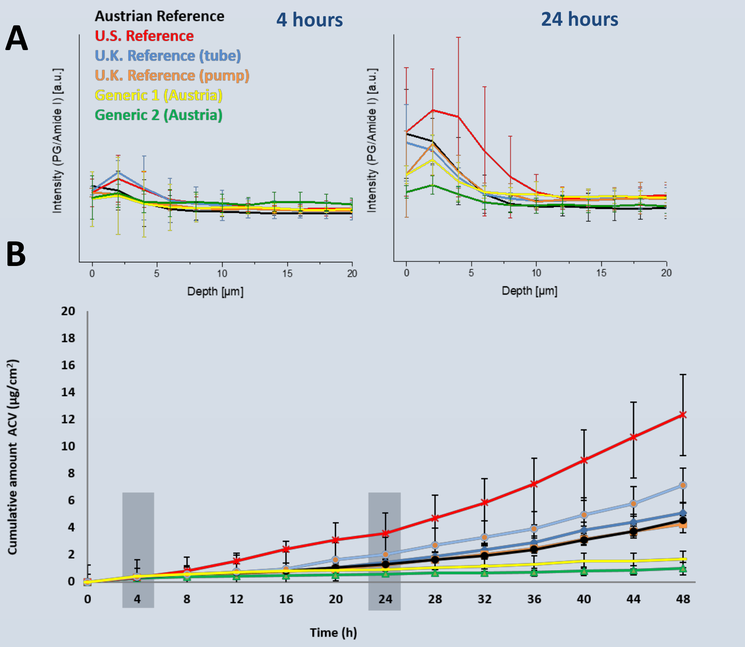


Figure 4: Penetration profiles of propylene glycol acquired with Raman microscopy (A, n=6) and permeation of acyclovir assessed via Franz cell IVPT studies (B, n=9). Values are displayed as mean ± SD.

Conclusions

- Confocal Raman microscopy allowed for a successful characterization of semisolid topical products by visualizing differences between international reference acyclovir creams and generic products from Austria.
- Mechanical stress induced by pumping of the U.K. reference cream during dispensing, influences microstructure of the cream compared to the same product dispensed from a tube.
- Epidermal penetration profiles of the creams studied by confocal Raman microscopy monitoring the propylene glycol component of the cream appeared to correlate with acyclovir permeation studied using IVPT studies.
- The novel approaches reported here allow for direct insights into the interaction of topical products with skin, and show how complementary, orthogonal approaches can be utilized to characterize topical product performance.

ACKNOWLEDGEMENT

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References

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