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abstract

Dandruff is a global phenomenon and the need for cosmetic products to relieve symptoms like flaking, itching and redness remains high [1]. Anti-dandruff consumer products in the cosmetics market typically rely on the use of strong anti-fungal ingredients. Three conventional actives are commonly used from a global perspective: zinc pyrithione, climbazole and piroctone-olamine. Except for a limited selection of multifunctionals, some blends or natural extracts, there has been no major new active launched to market for decades. In this article we present an entirely new solution: propanediol caprylate (Crinipan® PMC *green*), a novel molecule for cosmetic applications, developed to serve multiple needs: comparable efficacy to conventional anti-dandruff actives, natural origin, green chemistry, sustainability, new mode of action and simple formulating.

Introduction

Dandruff control can be characterized by the use of three conventional ingredients: zinc pyrithione, climbazole (Crinipan® AD) [2, 3] and piroctone-olamine. All three actives are primarily effective against the yeast *Malassezia spp.* that is linked to dandruff formation, and all have been used in the personal care market for decades. Even though they are typically not used specifically for preservation, all three established actives are part of the European Cosmetics Regulation (EC) No 1223/2009 *list of preservatives allowed in cosmetic products* (Annex V). This is a rather historical classification reflecting the active's anti-fungal properties that would surely contribute to preserve a product, but the main reason for use is a result of the active's antimicrobial properties, specifically controlling *Malassezia* on the scalp and thus reducing dandruff formation. It is not a requirement for an anti-dandruff agent to be part of a preservative list in terms of European law. Some multifunctional ingredients are also worth mentioning: Decylene glycol (SymClariol®), for example, is not an established active for dandruff control, though several reports on its positive effects for scalp care have been published [4, 5].

Globally speaking, *anti-dandruff* is considered a cosmetic claim not subject to particular regulation, but there are some exceptions. Two examples for more strictly regulated markets are the US and Japan. In the US, out of the three mentioned conventional actives, only zinc pyrithione is positively listed on the OTC drug monograph by the Food and Drug Administration (FDA) and therefore used in the North American market as an active [6]. In Japan, anti-dandruff products are considered quasi drugs (QD) [7]. Cosmetic manufacturers owning a QD-license have to apply for a premarket approval from the authorities before launching a new consumer product. The application has to demonstrate the safety of the product as well as appropriate anti-dandruff efficacy. In this regard manufacturers typically refer to the use of JSQI (Japanese Standards of Quasi-drug Ingredients) listed ingredients; one of these ingredients is *o*-cymen-5-ol (IPMP; SymOcide® C) [8]. *o*-Cymen-5-ol is also listed as a preservative, both in Europe (EU Cosmetics Regulation Annex V) and Japan (Japanese Standard for Cosmetics, Appendix 3). Looking at the molecule's physicochemical nature, its lipophilic properties suggest that it is a suitable active for skin benefits as well.

For formulators, ease of handling in the process of incorporating cosmetic actives into shampoos has always been a major consideration. Liquid actives simplify the formulation process significantly [2], because surfactant-based formulations are often made via cold process. Taking a look at the established actives, none of them is liquid: Zinc pyrithione is a surfactant-insoluble system, available as a dispersion. Thus zinc pyrithione is only found in cloudy shampoo formulations, while transparent shampoos are possible solely with surfactant-soluble actives such as climbazole and piroctone olamine. Though transparent shampoos can be made with climbazole and piroctone olamine, the pure actives are crystalline solids which need to be solubilized first.

It is known from literature that short to medium chain fatty acids also possess anti-fungal properties, but their practical use in cosmetics is limited by their intensive smell. Surprisingly, a nearly identical antimicrobial effect was reported for the ester derivatives [9]. Considering the relevance of an anti-*Malassezia* effect for reducing dandruff, a completely new ester-based anti-dandruff technology has been developed [10].

Serving the demand for new green solutions, we are presenting a modern, natural derived, anti-dandruff technology

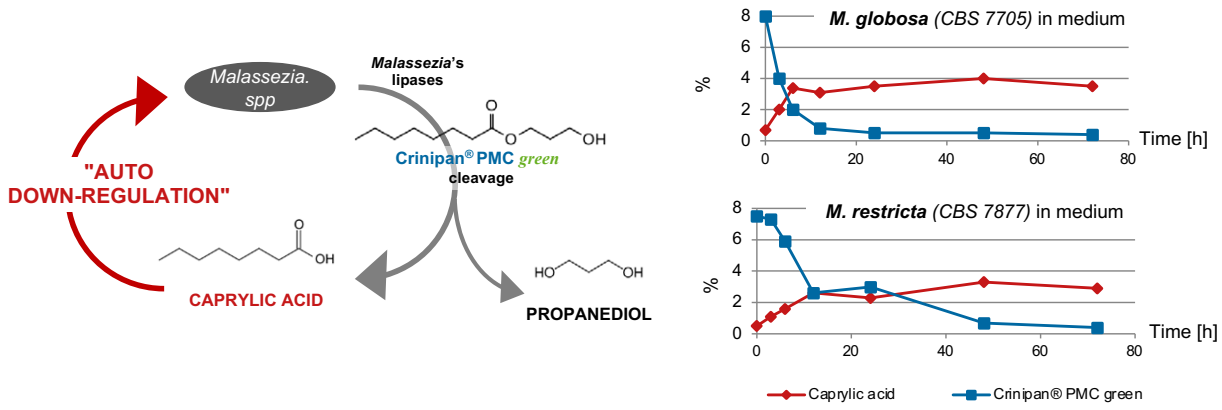

Fig. 1 Suggested mechanism for propanediol caprylate´s mode of action; Presence of *Malassezia spp.* "activates" propanediol caprylate to release the active caprylic acid.

with an innovative mode of action (**Fig. 1**). The activity of propanediol caprylate (Crinipan® PMC *green*) [11, 12] relies on *Malassezia's* natural dependence on triglycerides (esters) from sebum. The new liquid molecule [13, 14] propanediol caprylate works due to its similar chemical ester-structure: *Malassezia's* lipases cleave the ester to release the actual active (caprylic acid) that will in turn reduce *Malassezia* activity, leading to a reduction of dandruff. Propanediol caprylate is made by green chemistry from 100% plant-based feedstock.

Materials & Methods

Production Process

Propanediol Caprylate is a colorless and liquid ester that can be derived from natural materials like palm or palm kernel oil. Our objective was to produce propanediol caprylate using the 12 principles of green chemistry [15]. For this a green process with optimal atom economy was favored, including waste prevention, use of catalytic systems, non-hazardous materials, and low consumption of energy. Following this concept we first envisioned a trans-esterification [16], starting from ethyl caprylate and propanediol. Finally considering the broad variety of sustainable methods for direct esterification known today [17], a solvent-free esterification of caprylic acid and propanediol with even better atom economy was developed. This non-hazardous and energy efficient process generates only water as side product, clearly respects the green and sustainable chemistry principles, and leads to a natural origin index of 1 (ISO 16128) for Crinipan® PMC *green*.

Species	Strain
M. furfur	CBS 1878
M. sympodialis	CBS 7222, CBS 7979, ATCC 42132, DSM 6171
M. globosa	CBS 7966, PM1, CBS 7705
M. restricta	CBS 7877

Source: CBS = Centraalbureau voor Schimmelcultures, Utrecht, Nl; ATCC = American Type Culture Collection, Manassas, USA; DSM = Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig, D; The *M. globosa* wildtype strain PM1 was isolated and maintained by P. Mayser.

Tab. 1 *Malassezia* test strains.

Antimicrobial Efficacy against *Malassezia*

An agar dilution test was performed for nine *Malassezia* strains (**Tab. 1**) according to a procedure described by *Mayser* [9]. This included typical representative strains, known for dandruff formation on human skin (*M. globosa, M. restricta*). The strains were maintained on modified (m) Dixon-agar and testing was performed with mDixon agar including the respective test materials (caprylic acid, propanediol caprylate, control excluding antimicrobials).

Determination of Microbial Ester Cleavage

Ester cleavage of propanediol caprylate was investigated for the human associated species *M. globosa* and *M. restricta* (**Fig. 1**). A cell count of 0.5-2.5 × 10^5 CFU/µl was transferred to an agar plate, overlaid by propanediol caprylate and incubated at 32°C. After defined incubation times of 0, 3, 6, 12, 24, 48, and 72 h the supernatant was removed and the concentration of propanediol caprylate and caprylic acid determined by gas chromatography.

In vivo Study Assessing Reduction of Dandruff

In order to assess the dandruff reduction by propanediol caprylate on scalp from a typical rinse-off shower formulation, the product has been included in a standard clear sodium laureth sulfate based shampoo formulation. The evaluation was performed comparing to both positive and negative

Ingredients	Placebo	With Climbazole (Crinipan® AD)	With Propanediol Caprylate (Crinipan® PMC *green*)
Sodium Laureth Sulfate. Lauryl Glycoside	17	17	17
Citric Acid	0.15	0.15	0.15
Disodium EDTA	0.1	0.1	0.1
Water (Aqua)	76.55	76.05	76.05
Polyquaternium-10	0.2	0.2	0.2
Sodium Benzoate	0.5	0.5	0.5
Phenoxyethanol	0.5	0.5	0.5
Cocoamidoproyl Betaine	5	5	5
Anti-dandruff ingredient	0	0.5	0.5

Tab. 2 *In vivo* shampoo study; test shampoos.

Ingredients
Aqua
Cocamidopropyl Betaine
Decyl Glucoside
Sodium Cocoyl Isethionate
PEG-80 Sorbitan Laurate
PEG-150 Distearate
Glycerin
Citric Acid
Sodium Benzoate
Sodium Methyl Cocoyl Taurate
Parfum
Disodium EDTA
Polyquaternium-10

Tab. 3 *In vivo* Shampoo Study; Conditioning Phase; Mild wash-out shampoo from the market.

controls (**Tab. 2**): As positive control, the established anti-dandruff active climbazole was added to the shampoo base. As negative control, the shampoo base was used without addition of an active (placebo). In terms of the dose of the actives, climbazole was used at its established – known to be effective – dosage of 0.5%; propanediol caprylate was used at the same level. All shampoo formulations were applied unfragranced.

The study was started after a 14 days conditioning period in which the subjects were told to wash their hair only with a neutral shampoo (containing no actives) from the market (**Tab. 3**). The test shampoo application was performed 3 times per week, each time adhering to 3 minutes of incubation time on scalp.

The *in vivo* evaluation of dandruff flaking was performed by dermatologists on a 1 (no dandruff) to 5 (severe dandruff) scale, directly after the conditioning phase (baseline) and after 30 days of use (30 d). Additionally, an olfactory evaluation was done by the subjects to investigate a potential odor from caprylic acid formation.

Physicochemistry: Effect on Foam and Sensorial Properties

Anti-dandruff actives are mainly used in surfactant based formulations. For the evaluation of propanediol caprylate on foam behavior, shampoo formulations containing 0.5 and 1.0 w/w% propanediol caprylate were tested. As negative control, the shampoo base was used without addition of active (placebo). The samples were investigated at Krüss GmbH by using the Dynamic Foam Analyzer DFA 100. After diluting with demineralized water (1:1 w/w%), the solutions were treated by applying a defined foam generation process. The bubble count was recorded for 20 minutes and images of the foam bubbles were taken after 500 s. Additionally, foam quality and sensorial tests were performed by 24 untrained panelists by using a shampoo containing 1.0% propanediol caprylate vs placebo. After a defined prewash procedure, 100 µl of shampoo were applied onto the back of the hand in random order, and the panelists assessed the product's foam volume and skin softening effect.

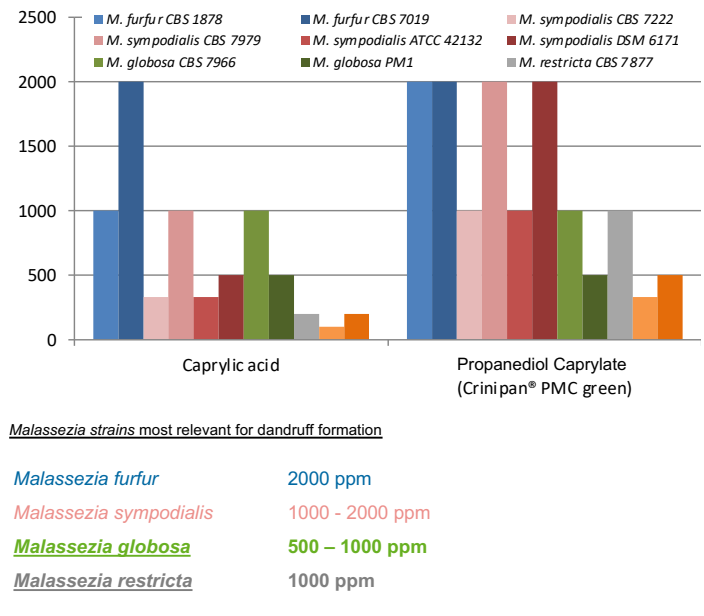

Fig. 2 The MIC values for propanediol caprylate are in a similar range as for caprylic acid. The efficacy of caprylic acid can be used for cosmetic purposes by applying its ester.

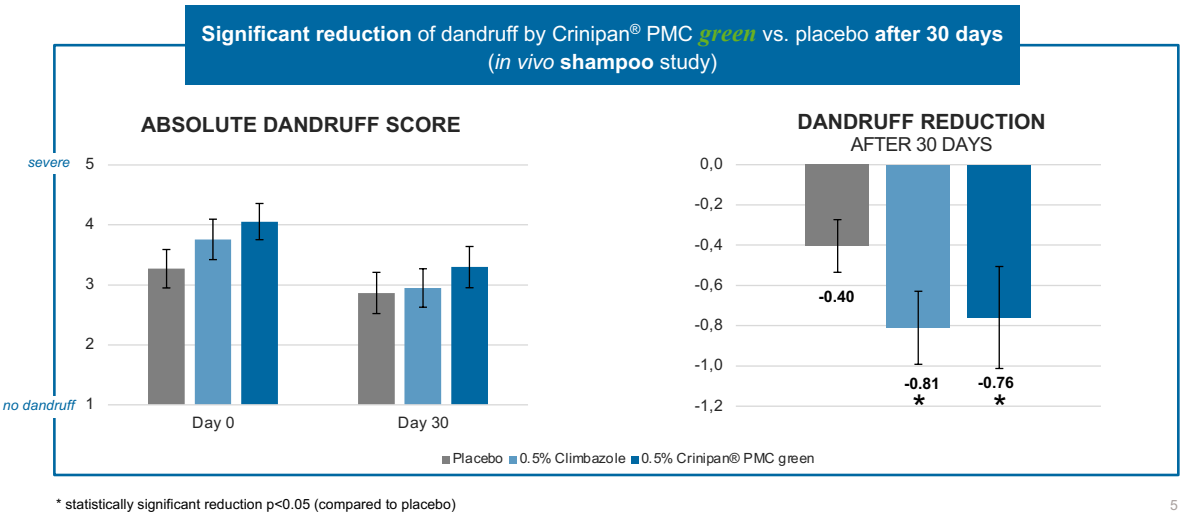

Fig. 3 Rinse off shampoo study: Propanediol caprylate reduces dandruff significantly in a 30 days study vs placebo and achieves comparable results to the established anti-dandruff benchmark climbazole.

Results

In vitro Efficacy

Caprylic acid is known for its antifungal activity but its strong odor limits topical application for cosmetics. Therefore, the respective ester, propanediol caprylate, was developed as anti-dandruff active. Similar antimicrobial activity is also detected for the odorless ester.

For this purpose, representative *Malassezia* strains were tested and minimum inhibitory concentrations (MIC) determined, which ranged from 500 to 2000 ppm. Especially for the dandruff associated species, particularly low values between 500 and 1000 ppm were found (**Fig. 2**).

The antimicrobial activity of propanediol caprylate is directly activated by the *Malassezia* fungus. Natural *Malassezia* lipases cleave the ester and release the actual active (caprylic acid). This activity has been confirmed *in vitro*. A significant decrease in concentration of propanediol caprylate was measured within hours of inoculation with the fungus with simultaneous increase of the concentration of caprylic acid (**Fig. 1**). The rate of conversion from propanediol caprylate to caprylic acid can be increased by adding higher numbers of cells.

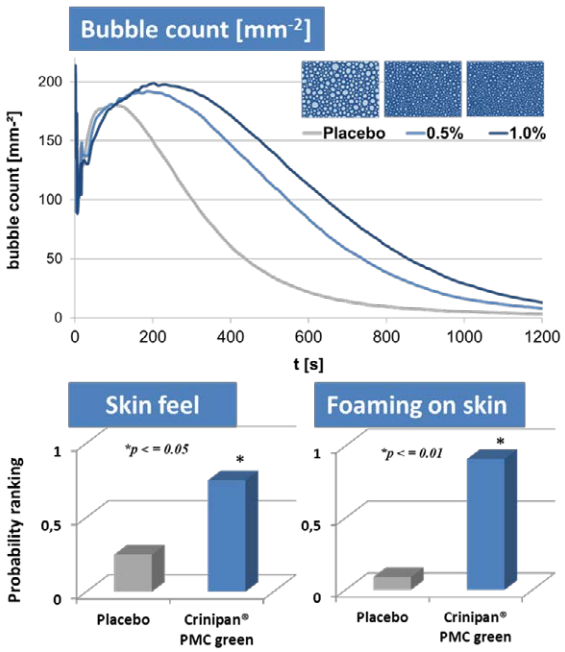

Fig. 4 Physicochemical behavior: Propanediol caprylate improves foam and sensorial experience on skin.

In vivo Efficacy

A statistically significant reduction on the absolute dandruff score versus placebo was found for the two actives propanediol caprylate and climbazole (positive control) in an *in vivo* rinse-off shampoo study with 82 subjects split into three groups respectively. Notably the addition of the new molecule, propanediol caprylate, to a shampoo leads to parity in effectiveness to the established active climbazole (**Fig. 3**).

Physicochemistry: Effect on Foam and Sensorial Properties

The addition of propanediol caprylate to shampoo formulations leads to a significantly smaller bubble size, but higher bubble count vs. placebo. This effect indicates an increased foam stability and leads to improved cleaning properties and better skin feel. The results were confirmed *in vivo* on wet skin: 91% of panelists reported a higher foam volume during shampoo application containing propanediol caprylate. Furthermore a softer skin feel was confirmed by 75% of the panelists vs. placebo (**Fig. 4**).

Conclusion

Propanediol caprylate represents a novel and effective anti-dandruff technology that is able to compete with conventional actives. The efficacy is based on caprylic acid's activity, but can be achieved by use of the ester technology. Use of this liquid ester comes with ease in handling as well as additional physicochemical benefits on foam quality and skin feel but bypasses disadvantages of the acid, such as a bad odor profile. Propanediol caprylate is made by green chemistry from 100% plant based feedstock. This satisfies the increasing demand for sustainability and naturalness in personal care.

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