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Silicone developmental formulations addressing performance challenges of acne indication

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Introduction

Acne is a common skin disease that occurs when hair follicles become clogged with dead skin cells and oil from skin. Causes are attributed to sedentary lifestyle and unhealthy food habits leading to hormonal problems, which trigger the development of acne. Lack of sleep, emotional and workrelated stress, smoking, drug abuse, and alcohol consumption are major triggers for the occurrence of acne among teenagers and adults. Acne has been estimated to affect 660 million people globally, making it the eighth most common disease worldwide. Many treatment options are available, including various topical and systemic therapies^[1,2].

The global acne product market is expected to grow steadily at a compound annual growth rate (CAGR) of approximately 3% between 2016 and 2020^[3]. The availability of over-the-counter (OTC) products and the preference for alternative therapies for treating acne have been restricting the sales of branded acne products. Renewed interest from biotech and pharmaceutical companies looking to develop products aimed at fulfilling these needs is predicted.

Creating topical formulations for acne management using silicone material offers the following benefits:

- Allows multiple forms and textures of over-the-counter (OTC) healthcare formulations, such as gels, sprays, lotions, patches and creams
- Allows enhancement of formulations with different benefits
 - Proven aesthetics and functional film characteristics, such as breathability and substantivity

- Enhanced spreading and sensory properties
- Low greasiness and tack; reduced tackiness; soothing and smooth feel
- Long-lasting effects

Silicones are non-comedogenic, non-acnegenic and mostly nonirritating. Each formulation needs to be tested and evaluated for its specific properties. There is a wide range of ingredients, and whether a product can be considered non-comedogenic/nonacnegenic will depend on ingredient type, usage level and skin type. Silicones also do not promote bacterial or other microbial growth^[4,5,6,7]. However, they can improve the diffusion and bioavailability of some actives.

Innovative formulation concepts that are dedicated to acne and demonstrate drug release and skin benefits – including nonocclusive and long-lasting properties and desired aesthetics – are highlighted in this paper. These formulations have been developed utilizing only salicylic acid as the chosen active ingredient.

Regulatory: FDA OTC monographs

OTC drug monographs are similar to a "recipe book" and are developed by the U.S. Food and Drug Administration (FDA). They define the safety, effectiveness and labeling of all marketed OTC active ingredients.

Companies can make and market an OTC product without FDA preapproval, and new products that conform to an OTC monograph may be marketed without FDA review. Those that do not conform must be reviewed by the New Drug Application process.

The final rule lists all permitted active ingredients for OTC topical acne products and their permissible concentrations and combinations:

- Salicylic acid in concentrations of 0.5% to 2%
- Benzoyl Peroxide in concentrations of 2.5% to 10%
- Sulfur in concentrations of 3% to 10%



The OTC monograph does not specify the vehicle composition. All concept formulations in this paper comply with the OTC monograph for acne^[8].

To serve customers with the appropriate product offerings, DuPont provides different product lines to meet increasing regulatory requirements and documentation. The silicones selected for this study fall under the Liveo[™] Topical Ingredient product line and were developed to fulfill current regulatory demands for consumer healthcare products, which are subjected to less regulation than approved drug products. During development and commercialization of the Topical Ingredient portfolio, enhanced quality and supply chain requirements were applied to a range of silicone technologies, including silicone fluids, elastomer blends, gum blends, resins, silicone organic waxes and emulsifiers. The new topical offering enables innovation for a variety of product forms and textures and provides enhanced spreading and sensory characteristics with long-lasting effects. Combined with enhancements for quality, supply chain security and traceability, and regulatory documentation, this offering supports customer innovation and regulatory compliance needs.

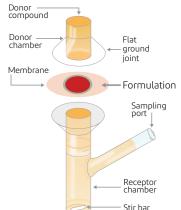
Performance evaluation methods

In vitro release of active

The active ingredient in the formulations, salicylic acid, needs to be delivered to the skin in order to get the therapeutic benefit for which it is intended. The release experiment was performed using a manual Franz diffusion cell console unit (System 912-SCT-24S, Model FDC24, Logan Instruments Corporation, Somerset, NJ) (see Image 1) at 32°C for a period of 6 hours (h). Polyether sulfone membrane (PES, 0.22 µ pore size, Millipore Corporation, Billerica, MA) was used as the membrane. Phosphate buffered saline (PBS, pH 7.4) solution was used in the receptor chamber. The permeation area of the Franz cell was 0.63 cm², and the cell volume was 5 mL. Sample collection was performed at 0.5, 1, 2, 4 and 6 h and replaced with fresh PBS. All samples were collected in amber vials, capped and analyzed using Waters[®] ACQUITY UPLC[®] system (Waters Corporation, Milford, MA) to assay salicylic acid.

Image 1: Left – Franz diffusion cell console unit (manually operated); right – single Franz cell





In vitro skin permeability testing

The *in vitro* permeability of salicylic acid was assessed for some of the formulations through dermatomed piglet skin tissues using a receptor medium made of acetate buffer pH 5.5. Experiments were carried out over a 20 h period, and diffusion cells were sampled every hour via a Logan 912 auto-sampler system with volume replacement. Temperature was set to 32°C. Permeated samples were analyzed by a Waters[®] ACQUITY UPLC[®] system. For each formulation, the dose was 8.5 mg/cm². Drug content was 2% over a permeation area of 1.77 cm².

At the end of the experimental period, the different skin layers – which include stratum corneum, epidermis and dermis – were separated for salicylic acid recovery analysis. All samples were analyzed to determine salicylic acid content, using a Waters[®] ACQUITY UPLC[®] system.

Sensory evaluation

The sensory evaluation for skin care products was designed to provide a sensory profile of select formulations assessed individually and rated versus one another, evaluated by an experienced panel. All sensory data were analyzed using critical response tables with significance for α <0.05.

The formulations were applied on the forearm of each panelist to evaluate the following:

- Before absorption wetness, spreadability, tackiness and perception of absorption rate
- After absorption gloss, film residue, greasiness, smoothness, tackiness and slipperiness

Payne cup measurement of water vapor permeability

Moisturization of the skin is accomplished by increasing its water content. This can be done by occlusion, which prevents the loss of water vapor from the skin. The water vapor permeability test used a collagen membrane covered with a thin layer of tested material. The test sample was then placed over a stainless steel cup loaded with water, and the cup was stored in a controlled-temperature location and regularly weighed to measure the amount of water loss. All tests were carried out in triplicate. Error bars represent ±SD (standard deviation). A higher percentage value indicates greater permeability and less occlusivity to water vapor.

Substantivity versus time

The substantivity of silicone on skin was evaluated versus time to assess the long-lasting effect of silicone-based formulations. The substantivity was assessed directly on each panelist's forearm. Detection was determined using an infrared spectrophotometer with Fourier transform attenuated total reflection (ATR) equipped with a skin analyzer device.

Concept 1 – Spot Acne Treatment

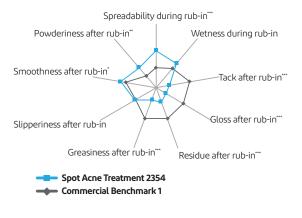
Concept 1, Spot Acne Treatment (reference 2354) is medicated with 2% salicylic acid. Acne spot treatments are over-thecounter acne products that help to heal pimples. Unlike other types of acne treatments, they are meant to be used only on existing blemishes. Spot treatment can be worn overnight or during the day, depending on consumer preference and visibility of the product. The aim is to quickly treat and diminish the existing pimple.

Table 1: Composition of Spot Acne Treatment 2354

Chemical/trade name	Chemical description	% w/w
Phase A		
Propylene Glycol	Propylene Glycol	40
Salicylic Acid	Salicylic Acid	2
Phase B		
W/Si emulsifier	PEG-10 Dimethicone	2
Liveo™ TI-1050, Fluid, 10 cSt	Dimethicone	10
Silicone Gum Blend	Dimethicone (and) Dimethicone Crosspolymer	13
Phase C		
Water	Water	31
Sodium Chloride	Sodium Chloride	1
Phenoxyethanol (and) Ethylhexylglycerin	Phenoxyethanol (and) Ethylhexylglycerin	1

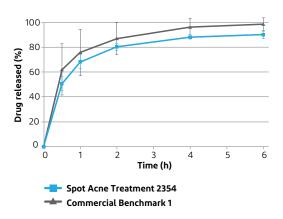
A sensory evaluation of Spot Acne Treatment 2354 and Commercial Benchmark 1^[9] containing salicylic acid at 2% was conducted. Based on the test performed, Spot Acne Treatment 2354 showed better spreadability and reduced tack, gloss, residue and greasiness, with more smoothness and more powderiness, compared to the commercial benchmark.

Figure 1: Sensory data for Spot Acne Treatment 2354



*Significant difference at 95% **Significant difference at 99% ***Significant difference at 99.9% Spot Acne Treatment 2354 demonstrated a salicylic acid release profile similar to that of the benchmark, as shown in Figure 2.

Figure 2: Salicylic acid release profile of Spot Acne Treatment 2354



Concept 2 – Acne MatteSerum

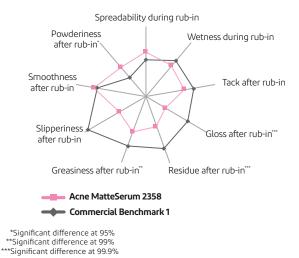
Acne serums usually are rich and have a heavier feel than moisturizing day cream, resulting in longer-lasting presence on the skin. Concept 2, Acne MatteSerum (reference 2358), is medicated with 2% salicylic acid.

Table 2: Composition of Acne MatteSerum 2358

Chemical/trade name	Chemical description	% w/w
Phase A		
Propylene Glycol	Propylene Glycol	35
Salicylic Acid	Salicylic Acid	2
Phase B		
W/Si emulsifier	PEG-10 Dimethicone	5
Liveo™ TI-1050, Fluid, 1.5 cSt	Dimethicone	10
Liveo™ TI-3021 Silicone Elastomer Blend	Dimethicone (and) Dimethicone Crosspolymer	5
Silicone Gum Blend	Dimethicone (and) Dimethiconol	5
Phase C		
Water	Water	31
Sodium Chloride	Sodium Chloride	1
Glycerin	Glycerin	5
Phenoxyethanol (and) Ethylhexylglycerin	Phenoxyethanol (and) Ethylhexylglycerin	1

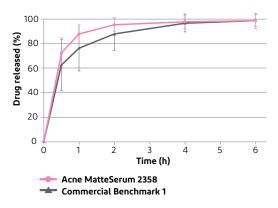
Figure 3 shows the sensory results of Acne MatteSerum 2358 evaluated against Commercial Benchmark 1 containing salicylic acid at 2%. Based on the test performed, Acne MatteSerum 2358 showed reduced tack, gloss, residue and greasiness, with more slipperiness and more powderiness, compared to the commercial benchmark.

Figure 3: Sensory data of Acne MatteSerum 2358



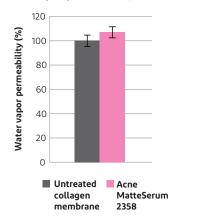
Acne MatteSerum 2358 demonstrated a salicylic acid release profile similar to that of the benchmark, as shown in Figure 4.

Figure 4: Salicylic acid release profile of Acne MatteSerum 2358



Acne MatteSerum 2358 shows non-occlusive properties, as demonstrated in Figure 5.

Figure 5: Water vapor permeability of Acne MatteSerum 2358



Note: Untreated non-occlusive collagen membrane is set as a control at 100%.

Concept 3 – Spotless Treatment Spray

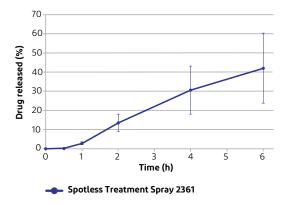
Concept 3, Spotless Treatment Spray (reference 2361), was designed to treat acne on large areas, such as the back or chest. Spotless Treatment Spray 2361 is medicated with 2% salicylic acid and is fast-drying and long-lasting.

Table 3: Composition of Spotless Treatment Spray 2361

Chemical/trade name	Chemical description	% w/w
Phase A		
Caprylic/Capric Triglyceride	Caprylic/Capric Triglyceride	16
Salicylic Acid	Salicylic Acid	2
Ethyl Alcohol 200 Proof	Ethyl Alcohol 200 Proof	21
Phase B		
Liveo™ TI-1010 Fluid, 1 cSt	Octamethyltrisiloxane	46
Liveo™ TI-7012 Solid Resin	Trimethylsiloxisilicate	4.5
Liveo™ TI-1050 Fluid 100 cSt	Dimethicone	11.5

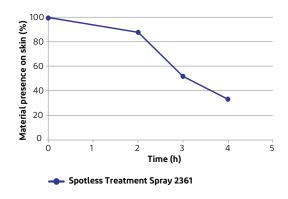
Spotless Treatment Spray 2361 demonstrated about 40% salicylic acid release in about 6 h, as shown in Figure 6.

Figure 6. Salicylic acid release profile of Spotless Treatment Spray 2361



Spotless Treatment Spray 2361 showed about 30% material presence on the skin, even after 4 h, as shown in Figure 7.

Figure 7. Substantivity evaluation of Spotless Treatment Spray 2361



Concept 4 - Invisible Acne Films

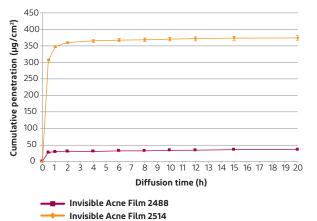
Concept 4 is based on the development of a formulation containing salicylic acid and tea tree essential oil that forms an invisible and comfortable film on the skin. This concept avoids the drawbacks of patches, such as visibility and potential discomfort. In these two Invisible Acne Film formulations (references 2488 and 2514), the amount of salicylic acid is kept the same in each formulation, based on solid content.

Table 4: Composition of Invisible Acne Films 2488 and 2514

Chemical/trade name	Chemical description	2488 % w/w	2514 % w/w
Phase A			
Alcohol	Ethyl Alcohol 200 Proof	20	20
Salicylic Acid	Salicylic Acid	0.14	0.64
Phase B			
Liveo™ TI-1010 Fluid, 0.65 cSt	Hexamethyldisiloxane	68.86	46.36
Liveo™ TI-7012 Solid Resin	Trimethylsiloxysilicate	7	7
Phase C			
Liveo™ TI-2021 AMS Specialty Fluid	Caprylyl Methicone	3	3
Tea Tree Essential Oil	Melaleuca Alternifolia Leaf Oil	1	1
Liveo™ TI- 1010 Fluid, 10 cSt	Dimethicone	-	7
Medium-Chain Triglyceride	Caprylic/Capric Triglyceride	-	15

As shown in Figure 8, the composition of the formulation has an impact on the release of the active. The presence of the silicone fluid and medium-chain triglycerides in the formulation impacts the release of salicylic acid. Invisible Acne Film 2514 with silicone fluid and medium-chain triglycerides allows the release of salicylic acid. Invisible Acne Film 2488 shows limited release of the active.

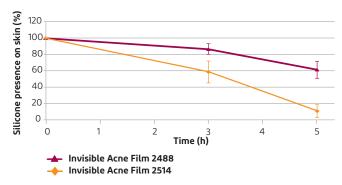
Figure 8: Salicylic acid cumulative penetration by Invisible Acne Films 2488 and 2514



As shown in Figure 9, the presence or absence of silicone fluid and medium-chain triglycerides in the formulation impacts the substantivity of the Invisible Acne Film.

Invisible Acne Film 2488 shows good substantivity, with 85% of silicone remaining on the skin after 3 h and 60% remaining after 5 h. Invisible Acne Film 2514 based on silicone fluid and medium-chain triglycerides shows moderate substantivity, with 60% of silicone remaining on the skin after 3 h and 10% remaining after 5 h.

Figure 9: Substantivity versus time of Invisible Acne Films 2488 and 2514



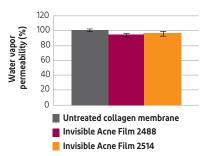
Invisible Acne Film 2514 with silicone fluid and medium-chain triglycerides demonstrated a smoother, greasier and tackier feel on the skin versus Invisible Acne Film 2488, as shown in Figure 10.

Figure 10: Sensory evaluation of Invisible Acne Films 2488 and 2514



Invisible Acne Films 2488 and 2514 demonstrated non-occlusivity; both formulations allowed the skin to breathe, as shown in Figure 11.

Figure 11: Water vapor permeability of Invisible Acne Films 2488 and 2514



Note: Untreated non-occlusive collagen membrane is set as a control at 100%.

Concept 5 – Acne Lotions

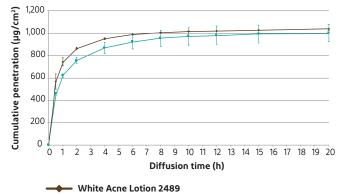
A lotion is a liquid product that is thin enough to be spread over the skin easily. Generally, lotions have a light feel on the skin – reducing the impression of greasiness during application, which is an important attribute for acne treatment. Thick lotions or creams can provide the impression of pore-clogging to the patient. The aim of Concept 5 is to develop lotions with salicylic acid that are either white or clear/transparent (references 2489 and 2490, respectively) according to the ratio between the different ingredients.

Table 6: Composition of White Acne Lotion 2489 and Transparent Acne Lotion 2490

Chemical/trade name	Chemical description	2489 % w/w	2490 % w/w
Phase A			
W/Si emulsifier	PEG-10 Dimethicone	6	6
Liveo™ TI-2021 AMS Specialty Fluid	Caprylyl Methicone	20	20
Liveo™ TI-3021 Silicone Elastomer Blend	Dimethicone and Dimethicone Crosspolymer	5	5
Phase B			
Salicylic Acid	Salicylic Acid	2	2
Propylene Glycol	Propylene Glycol	20	46
Phase C			
Water	Water	44.94	18.49
Sodium Chloride	Sodium Chloride	1	1
NEOLONE™ PH-100 Preservative	Phenoxyethanol	0.83	0.83
Caprylyl Glycol	Caprylyl Glycol	0.68	0.68

Both White Acne Lotion 2489 and Transparent Acne Lotion 2490 performed equally in releasing the active. Salicylic acid release from the lotions was not strongly impacted by the change of ingredient ratios in the formulations, as shown in Figure 12.

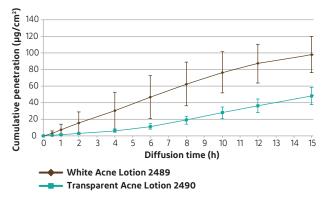
Figure 12: Salicylic acid release profile of White Acne Lotion 2489 and Transparent Acne Lotion 2490



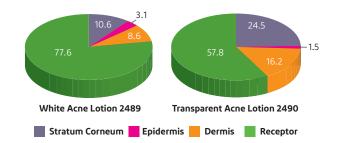
Transparent Acne Lotion 2490

Faster penetration is observed when salicylic acid is formulated in White Acne Lotion 2489. The salicylic acid distribution profile in each skin layer differs between White Acne Lotion 2489 and Transparent Acne Lotion 2490. Salicylic acid concentrations observed in the stratum corneum and dermis were higher for Transparent Acne Lotion 2490.

Figure 13: Salicylic acid penetration profile of White Acne Lotion 2489 and Transparent Acne Lotion 2490 using dermatomed piglet skin

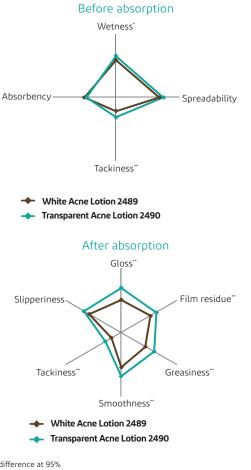


Figures 14 and 15: Distribution profile of salicylic acid by White Acne Lotion 2489 and Transparent Acne Lotion 2490 in dermatomed piglet skin



In terms of sensory profile, Transparent Acne Lotion 2490 demonstrates a higher film presence and smoother feel and is greasier and tackier with a less mattifying effect compared to White Acne Lotion 2489, as shown in Figures 16 and 17.

Figures 16 and 17: Sensory evaluation of White Acne Lotion 2489 and Transparent Acne Lotion 2490

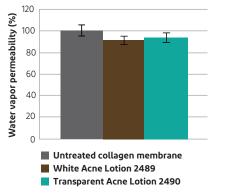


*Significant difference at 95% **Significant difference at 99%

***Significant difference at 99.9%

Both lotions demonstrate non-occlusive properties, allowing the skin to breathe.

Figure 18: Water vapor permeability of White Acne Lotion 2489 and Transparent Acne Lotion 2490



Note: Untreated non-occlusive collagen membrane is set as a control at 100%.

Concept 6 – Light Acne Cream

Formulations with high levels of silicone are sometimes perceived by the user as greasy and heavy. The aim of Concept 6 is to develop a silicone-based cream with a light feel. Light Acne Cream (reference 2491) is loaded with 2% salicylic acid to treat acne.

Table 6: Composition of Light Acne Cream 2491

Chemical/trade name	Chemical description	% w/w
Phase A		
W/Si Emulsfiier	PEG-10 Dimethicone	3.00
Liveo™ TI-2021 AMS Specialty Fluid	Caprylyl Methicone	12.00
Phase B		
PEG 400	PEG-8	10.00
Salicylic Acid	Salicylic Acid	2.00
Phase C		
Water	Water	71.49
NEOLONE™ PH-100 Preservative	Phenoxyethanol	0.83
Caprylyl Glycol	Caprylyl Glycol	0.68

Light Acne Cream 2491 demonstrates similar performance compared to Commercial Benchmark 2^[10] in releasing salicylic acid. The level of salicylic acid in the benchmark is 1%, whereas Light Acne Cream 2491 contains 2% salicylic acid.

This is highlighted in Figure 19, which shows the percentage of applied dose released from the formulation.

Figure 19: Cumulative profile of salicylic acid by Light Acne Cream 2491

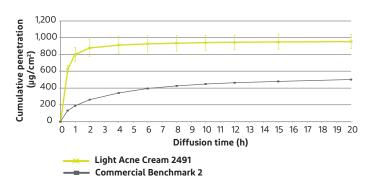
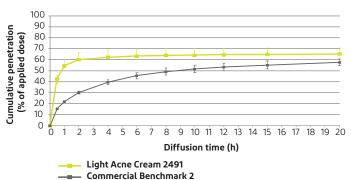


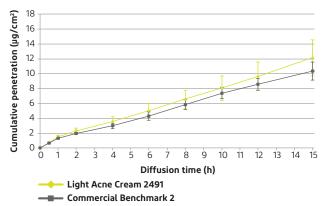
Figure 20: Cumulative release of salicylic acid by Light Acne Cream 2491



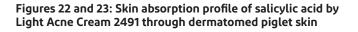
The same penetration rate is observed for both Light Acne Cream 2491 and the benchmark. The distribution profiles in the skin are similar.

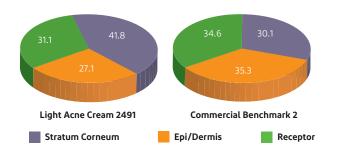
Figures 24 and 25: Sensory evaluation of Light Acne Cream 2491

Figure 21: Penetration profile of salicylic acid by Light Acne Cream 2491

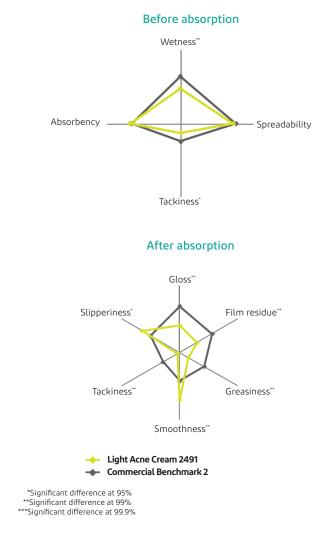


Both lotions demonstrate non-occlusive properties, allowing the skin to breathe.





In terms of sensory profile, Light Acne Cream 2491 demonstrates a mattifying effect, reduced tackiness, a greasier and smoother feel, higher film presence, and a slipperier feel versus the benchmark.



Concept 7 – Acne Patch

The aim of this development is to create a small patch loaded with 2% salicylic acid based on the formulation composition that is dedicated to acne treatment and spot camouflage. This concept was developed under the name Protective Acne Patch. The patch was manufactured and packaged by Vektor Pharma (vektorpharma.com).

Table 7: Composition of Protective Acne Patch

Chemical/trade name	Chemical description	% w/w
Salicylic Acid	Salicylic Acid	2
Liveo™ BIO-PSA 7-4602 Silicone Adhesive	Ethyl Acetate and Trimethylsiloxysilicate/ Dimethiconol Crosspolymer	88
Solvent/formulation aid	See list below (cont. on pg 9)	10

The following silicone and non-silicone materials can potentially be used as excipients, solvents (separately or blended), or penetration-enhancers in the formulation of a patch^[11,12]:

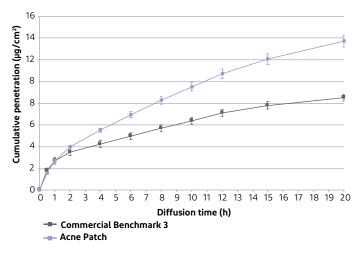
- Dimethicone
- Alkanes (e.g., isododecane, isooctane, etc.)
- Alcohols, fatty alcohols and glycols (e.g., propylene glycol, PEG 300, oleyl alcohol, Transcutol P), acetic esters (e.g., ethyl acetate, n-butyl acetate, etc.)
- Glycerin
- · Esters (e.g., isopropyl myristate, isopropyl palmitate)
- Fatty acids (e.g., oleic acid)
- Surfactants (e.g., silicone polyethers)
- Other types of polymers (e.g., polyvinylpyrrolidone)

The Protective Acne Patch allows the release of salicylic acid.

Image 2: Acne patches

Cumulative release of salicylic acid by the Protective Acne Patch is higher than that of Commercial Benchmark 3^[13], as shown in Figure 26.

Figure 26: Cumulative release of salicylic acid by the Protective Acne Patch



Conclusion

The versatility of silicone chemistry in terms of functionalities and characteristics translated into an easy-to-use excipient toolbox for topical applications. A wide range of formulation options to load, stabilize and release various drugs for dermatological and local treatments is offered, as demonstrated by the different silicone formulations loaded with salicylic acid in this paper. Optimizing the efficiency of drug delivery and behavior of the formulations on skin certainly would lead to better perceived efficacy by the user, associated with a more pleasant sensory feel required for a specific skin disease. Such performance benefits potentially may increase patient compliance with treatment requirements. DuPont Healthcare Solutions offers a wide range of innovative silicone materials for formulators to consider when developing new drug products for acne treatment.

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- V. Caprasse, M. Eeman, T. Gorski, F. Lin, and K. Ulman, Silicone materials for topical applications: Meeting the specialized needs of evolving market and regulatory requirements Liveo Corporation publication # 52-1253-01.
- 9. Commercial Benchmark 1 Active Ingredient: Salicylic Acid (2.0%). Inactive Ingredients: Aqua (Water, Eau), Caprylic/Capric Triglyceride, Glycerin, Salix Nigra (Willow) Bark Extract, Stearyl Alcohol, Cetyl Alcohol, Glyceryl Stearate SE, Cera Alba (Beeswax, Cire D'Abeille), Calophyllum Inophyllum Seed Oil, Cymbopogon Schoenanthus Extract, Dipotassium Glycyrrhizate, Equisetum Hiemale Extract, Hamamelis Virginiana (Witch Hazel) Leaf Extract, Humulus Lupulus (Hops) Extract, Hydrastis Canadensis (Goldenseal) Extract, Lonicera Caprifolium Extract, Lonicera Japonica Extract, Simmondsia Chinensis (Jojoba) Seed Oil, Stearic Acid, Sorbic Acid, Tocopherol, Xanthan Gum, Lecithin, Glucose, Glycine Soja (Soybean) Oil, Parfum (Fragrance), Sodium Chloride, Glucose Oxidase, Lactoperoxidase, Phenoxyethanol, Citral, Geraniol, Limonene, Linalool.
- Commercial Benchmark 2 A medical device for the topical treatment of light to moderate acne. Composition: Glycolic Acid, Salicylic Acid, S-Carboxymethyl Cysteine, L-Lysine, Alpha Hydroxy Acid Esters (Malic and Citric). Excipients: emulsifiers, deionized and filtered water q.s. to 100.
- A. Bobenrieth, A-L. Girboux, P. Sivanand, X. Thomas, Rheology approach to assess the effect of formulating skin permeability enhancers with pressure sensitive silicone adhesives, presented at Association de Pharmacie Galénique Industrielle (APGI) annual meeting, 2016 APGI Meeting.
- L. Nartker, A-L. Girboux, A. Bobenrieth, X. Thomas, R. Huber, P. Sivanand, Rheology approach to assess the effect of formulating skin permeability enhancers with pressure sensitive silicone adhesives, presentation at American Association of Pharmaceutical Scientists (AAPS) annual meeting, October 2015, Orlando, Florida, USA.
- Commercial Benchmark 3 Inactive ingredients: Acrylates Copolymer, Sesamum Indicum Oil, Vinis Vinifera Extract, Melaleucal Alternifolia Oil, Eucalyptus Globulus Oil, Rosmarinus Officinalis Oil, Gaultheria Pocumbens Leaf Oil, Citrus Aurantium Dulcis Oil, Lavandula Augustifolia Oil, Salicylic Acid, Geraniol, Citral, Liminene, Linalool.

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