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Impact of Silicone Polymers on Corticosteroid Drug Delivery and Performance Testing

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Introduction

Topical applications are designed to treat various skin conditions and mainly marketed as prescription or consumer healthcare products. Prescription market requirements include safe and effective delivery of the API (active pharmaceutical ingredient) to efficiently achieve pharmacokinetic and clinical relevance. In contrast, the consumer healthcare market strongly favors the sensory aspects of a formulation; this includes efficacy with a pleasant feel to help patients be more compliant with their treatment.

The specific properties of silicone materials can play an important role in the development of innovative medicated products by allowing enhanced drug delivery and efficacy in topical applications yet sensory pleasing. Silicone materials are available as topical excipients in a wide range of forms – volatile, liquid, gel and elastomeric solid – which all benefit from the unique molecular behavior of polydimethylsiloxanes in terms of stability, permeability, surface and interface properties.

Benefits of Silicone Topical Excipients

Silicone materials are not only non-irritating and safe for topical applications, they have a pleasant feel on skin that makes patients more likely to comply with doctor's prescriptions. Many current excipients for topically applied pharmaceuticals are perceived by patients as too oily or otherwise unpleasant on skin. In fact, in some critical applications, such as the treatment of psoriasis, non-compliance with the prescribed treatment is a major issue. DuPont Liveo™ Healthcare (previously Dow Corning Healthcare) sponsored a survey of more than 250 patients topically treated for psoriasis and found that 70 percent did not properly follow the requirements of their prescriptions.

Silicone topical excipients do allow for easier spreadability and increased substantivity, as well as improve the efficacy of the treatment by enhancing the drug delivery to the targeted site. Their tunable compatibility with APIs may lead to a control of the drug diffusion and the skin penetration while providing formulators with formulation and processing flexibility.

Recent testing of silicone polymers for topical delivery of betamethasone dipropionate

This paper summarizes recent comparison testing of three silicone polymer types – a silicone fluid, a silicone gum blend and a silicone elastomer – for their efficacy in the delivery of betamethasone dipropionate (BDP). BDP is a widely used glucocorticoid in topical applications to treat inflammatory skin conditions including dermatitis, eczema and psoriasis.

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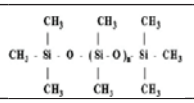
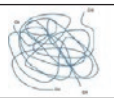
Study Conditions

Three silicone polymer types were considered for the three case studies based on their added benefits during formulation and to the healthcare application. They were respectively represented by Liveo™ Q7-9120 Silicone Fluid, 20 cSt, Liveo™ ST-Elastomer 10 and Liveo™ Dimethiconol Blend 20. Table 1 below compares the structure and benefits in topical applications of each polymeric excipients.

Table 1. Silicone polymer testing in topical drug delivery

	Silicone Fluid	Silicone Elastomer	Silicone Gum Blend
Commercial Name	Liveo™ Q7-9120 Silicone Fluid, 20 cSt*	Liveo™ ST Elastomer 10	Liveo™ Dimethiconol Blend 20
Structure (schematic drawing)			
INCI Name	Dimethicone	Cyclomethicone and Dimethicone Crosspolymer	Dimethicone and Dimethiconol
Description	Non-volatile silicone fluid (polydimethylsiloxane or PDMS)	Gel made of cross-linked silicone polymer (elastomer swollen with volatile silicone fluid (cyclomethicone)	High molecular weight OH terminated polydimethylsiloxane dissolved in non-volatile silicone fluid (PDMS)
Benefits in medical applications	• Skin protectant* • Non-occlusivity • Emolliency • Lubrication • Spreadability	• Non-occlusivity • Contributes to aesthetics properties: smooth, dry and silky feel • Rheology modifier to adjust formulation consistency	• Film forming agent • Non-occlusivity • Gives a more lubricious, long lasting after feel • Substantivity • Non-volatile diluent

**Skin protectant linked to the content of dimethicone at appropriate level for protectancy claim per the FDA monograph. Liveo™ Q7-9120 Silicone Fluid (Dimethicone NF) meets the requirements as a skin protectant for over-the-counter human drug products (FDA monograph 21 CFR, Part 347.10)*

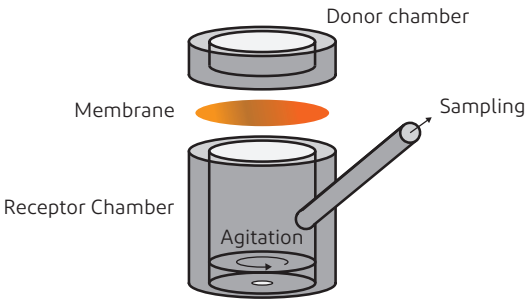
Drug delivery test methods

When formulating for pharmaceutical applications, the characteristics of the drug delivery profile are critical data to assess the efficacy of the product. For transdermal and topical drug delivery systems, DuPont uses the Franz diffusion cell method, whereby the device is equipped with a synthetic membrane or skin sample. This methodology allows to quantify the amount of drug which can diffuse outside the topical formulation matrix within time as well as the amounts which permeate through or are retained in the different skin layers.

In vitro release testing

The in vitro release testing of BDP was conducted at 32° Celcius using a polysulfone membrane and Franz cells with 11 mL receptor volume and 1.77 cm² release surface. The synthetic membrane was set in Franz cells filled with a receptor medium made of acetate buffer (pH 5.5) and isopropyl alcohol (70/30 weight ratio). For each formulation containing 0.064 weight percent of BDP, a dose of 50 mg/cm² was homogeneously applied onto the membrane. The test was done in triplicate for each formulation, meaning three cells per formulation. The experiment was carried out for 20 hours; a 1 mL sample was collected from the receptor chamber and replaced with fresh buffer solution every four hours: T1 = 4 h, T2 = 8 h, T3 = 12 h, T4 = 16 h, T5 = 20 h using a Logan 912 auto-sampler system. All samples were analyzed by liquid chromatography to determine BDP content, using a Water Acquity™ ultra-high performance liquid chromatography (UPLC) system.

Figure 1. Franz-Type diffusion cells



In vitro skin permeability testing

The in vitro skin permeability testing of BDP was performed through dermatome pig skin tissues. The Franz cells were set up as detailed in the previous paragraph for the in vitro release testing but with an applied dose of 7.5 mg/cm². The experiment was carried out for 20 hours and the cells were sampled every hour according to the in vitro release testing procedure.

After 20 hours, at the end of the diffusion period, a skin compartment analysis was performed by separating the different skin layers – stratum corneum, epidermis and dermis – and recovering the BDP retained in each layer. All samples, permeated into the receptor fluid or extracted from skin layers, were analyzed by UPLC as done for the in vitro release testing.

Performance on skin - Test methods

Sensory Evaluation

The sensory evaluation for skin care products is designed to provide a sensory profile of selected formulations assessed individually and rated versus one another, evaluated by an experienced panel. All sensory data are analyzed using critical response tables with significance for a<0.05.
The formulations are applied on the forearm of each panelist to evaluate the characteristics before and after absorption (absorption meaning perception of absorption by the panelist).

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

Water vapor permeability measured by Payne cup methodology

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 is based on Payne cup methodology; a collagen membrane is covered with a thin layer of the tested material. The collagen membrane supporting the tested material is then placed on top of a stainless steel cup partially filled with water to keep a headspace between the collagen membrane and the water surface. The cup is then stored for the duration of the test in an oven with controlled temperature and dry environment. All tests are carried out in triplicates.

Substantivity versus time or washes

The substantivity of silicone-based formulations on skin is evaluated versus time or washes in order to evaluate its durability, long lasting effect or wash off resistance. The test is performed by applying the formulations onto panelist forearms and the silicone staying on skin is detected and analyzed by infra-red spectroscopy using an attenuated total reflectance Fourier transform infrared spectrophotometer (ATR-FTIR) equipped with a skin analyzer device.

Evaluation of silicone based topical formulations containing BDP

To evaluate the impact of the different silicone polymers on the release of BDP, three water-in-oil (W/O) formulations were prepared as detailed in Table 2. They respectively contain the silicone fluid, the silicone elastomer and the silicone gum blend described in Table 1. The formulations were used in the following tests:

- In an in vitro drug release study, the cumulative drug release profiles of the three emulsions were compared together.
- The in vitro skin permeation study allowed to compare only the emulsions in pairs, as result silicone fluid based emulsion was successively compared to the one based on silicone elastomer and then to the other based on silicone gum blend.

Formulations

Table 2. Water-in-oil formulations

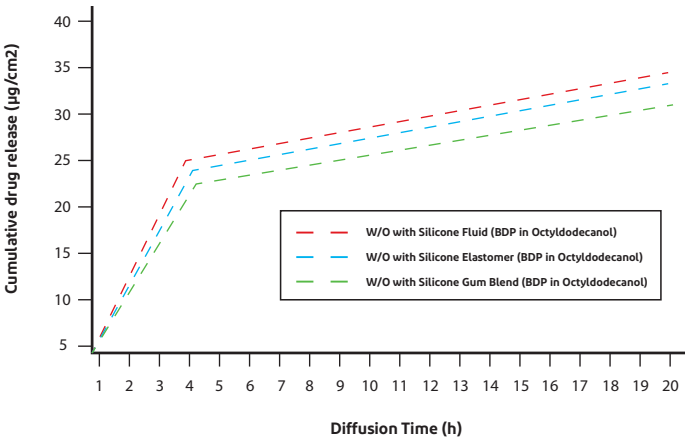
	W/O based on Silicone Fluid (W/O Fluid)	W/O based on Silicone Elastomer (W/O Elastomer)	W/O based on Silicone Gum Blend (W/O Blend)
Ingredients	**Weight %**	**Weight %**	**Weight %**
Liveo™ Q7-9120 Silicone Fluid, 20 cSt	5.0		
Liveo™ ST-Elastomer 10		5.0	
W/O Silicone Emulsifier	2.0	2.0	2.0
Betamethasone dipropionate (BDP)	0.064	0.064	0.064
Octyldodecanol	19.936	19.936	19.936
Water	72.0	72.0	72.0
Sodium chloride	1.0	1.0	1.0

Results

Drug diffusion

As shown in Figure 2 hereafter, the cumulative drug release results clearly indicate that the BDP release from the W/O formulations was not significantly impacted by the type of silicone polymers used in the W/O emulsions.

Figure 2. in vitro release of BDP from the W/O emulsions



If the in vitro drug release test did not allow to differentiate one silicone excipient from the other ones, the in vitro skin permeation studies gave more contrasting results as detailed in Tables 4 to 5 and Figures 3 to 8.

Skin permeation study of W/O Fluid formulation versus W/O Elastomer formulation

As detailed in Table 4, the cumulative diffusion of BDP was a little higher for the W/O emulsion based on the silicone fluid. After 20 hours roughly 1.5 time more BDP was diffused from this emulsion compared to one based on silicone elastomer: 21.7 percent of the BDP initially applied at the skin surface was found in the receptor medium and skin layers for the W/O Fluid formulation versus 14.2 percent for the W/O Elastomer formulation.

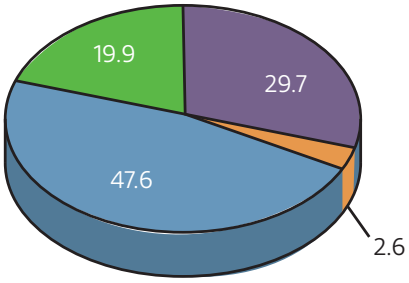
The slower diffusion of the BDP from the W/O Elastomer formulation was confirmed by the skin compartment analysis as shown in the Figures 3 and 4: a higher amount of BDP was found in the dermis for the W/O fluid formulation compared to W/O Elastomer formulation for which a higher BDP amount was retained in the stratum corneum.

Though the BDP skin permeation rate profiles for W/O Fluid and W/O Elastomer formulations were not significantly different, respectively 0.15 µg/cm² versus 0.11 µg/cm², a beginning of a plateauing effect starting after T = 16 h could be observed for the W/O Elastomer formulation (Figure 5), potentially induced by a slower release and higher retention of BDP in skin with this formulation.

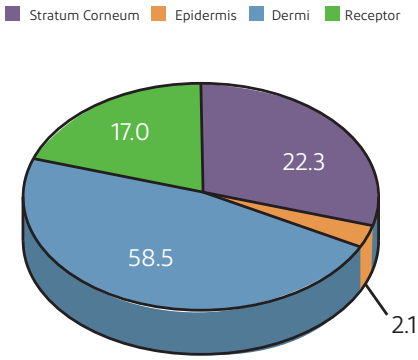
Table 4. Permeation studies: W/O Fluid versus W/O Elastomer formulations

	Receptor		Skin	Receptor + Skin
	Diffusion of BDP (µg/cm²)	Diffusion of BDP (%)	Diffusion of BDP (%)	Avg BDP (%)
W/O Fluid formulation	0.26	3.4	18.3	21.7
W/O Elastomer formulation	0.19	2.3	11.9	14.2

Figure 3 and 4 – Skin compartment analysis for W/O Fluid and W/O Elastomer formulations

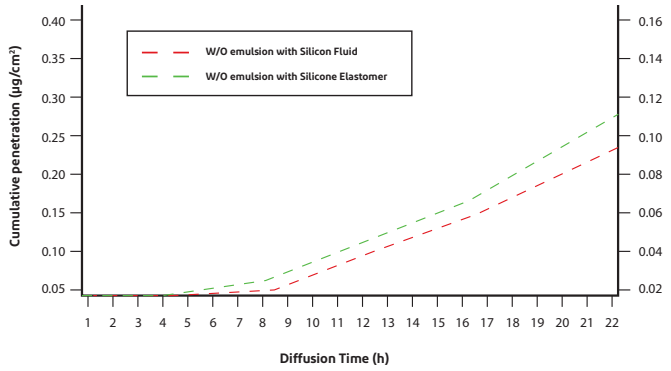


W/O with Silicone Elastomer

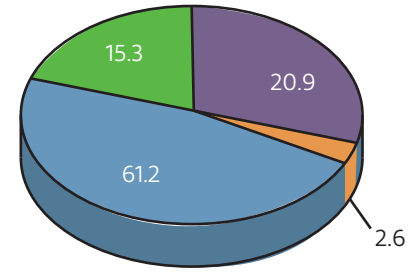


W/O with Silicone Fluid

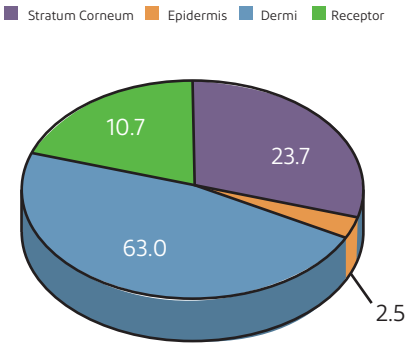
Figure 5. Permeation profile through pig skin



Figures 6 and 7. Skin compartment analysis for W/O Fluid and W/O Blend formulations



W/O with Silicone Gum Blend



W/O with Silicone Fluid

Skin permeation study of W/O Fluid formulation versus W/O Blend formulation

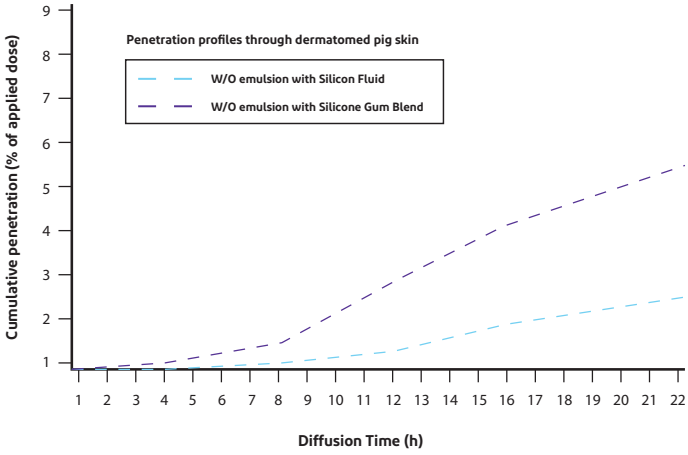
Detailed in the Table 5, the second permeation study showed only a slightly higher total diffusion rate of the BDP for the W/O Blend formulation with roughly 1.2 times more after 20 hours. The test showed 27.7 percent of the BDP in the recteptor medium and skin layers for the W/O Fluid formulation versus 33.1 percent for the W/O Blend formulation. However, this difference was not observed in the skin distribution, Figures 6 and 7 show similar repartition of BDP in each skin compartment after 20 hours.

As shown in Figure 8, the W/O Blend formulation would have a higher capacity to diffuse the BDP through the skin. The cumulative amount of BDP from water-in-oil emulsion with silicone fluid was around 0.19 µ after 20 hours compared to 0.39 µ for the formulation with silicone gum blend, respectively 0.11 µg/cm² versus 0.22 µg/cm²

Table 5. Permeation studies: W/O Fluid versus W/O Blend formulations

	Receptor		Skin	Receptor + Skin
	Diffusion of BDP (µg/cm²)	Diffusion of BDP (%)	Diffusion of BDP (%)	Avg BDP (%)
W/O Fluid formulation	0.19	2.3	25.3	27.7
W/O Blend formulation	0.39	4.9	28.2	33.1

Figure 8. Permeation profile through piglet skin



Performances on skin

The following performance evaluations were considered for the three W/O emulsions: occlusivity, sensory profile, substantivity versus time and washes. Because sensory and substantivity were performed as in vivo testing using panelists, the test samples had to be placebo and consequently W/O formulations were prepared without BDP as detailed in the Table 6.

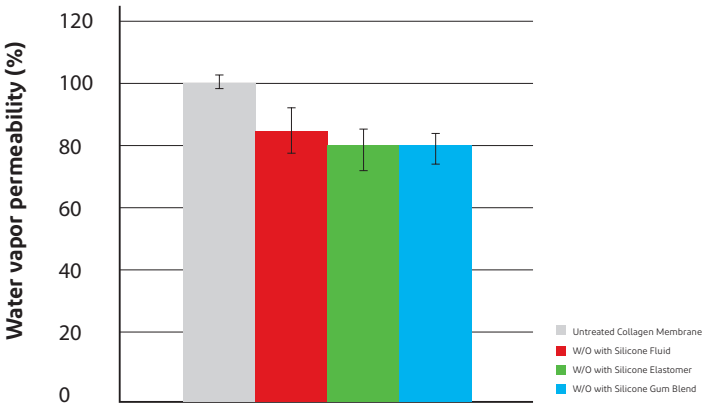
Table 6. Placebo formulations for in vivo evaluation

	W/O Fluid placebo	W/O Elastomer placebo	W/O Blend placebo
Ingrediants	Weight %	Weight %	Weight %
Liveo™ Q7-9120 Silicone Fluid, 20 cSt	5.0		
Liveo™ ST-Elastomer 10		5.0	
Liveo™ Dimethiconol Blend 20			5.0
W/O Silicone Emulsifier	2.0	2.0	2.0
Octyldodecanol Water Sodium Chloride	20.0	20.0	20.0
Water	72.0	72.0	72.0
Sodium Chloride	1.0	1.0	1.0

A) Occlusivity

As shown in Figure 9, the nature of the silicone polymer used in the W/O placebo formulations did not impact the occlusivity. The three formulations would be considered as non-occlusive.

Figure 9. Occlusivity performance for the W/O placebo formula formulations



B) Sensory Profile

As shown in the sensory evaluation summary graph (Figure 10), the W/O Fluid placebo resulted in a significantly less glossy, less greasy, less smooth feel and lower film presence compared to the two other emulsions W/O Elastomer and W/O Blend placebo. Between these last, no significant difference was observed as indicated by the score for W/O Elastomer and W/O Blend placebo in Table 7.

Table 7. Sensory evaluation score

	Gloss	Film Residue	Greasiness	Smoothness	Tackiness	Slipperiness
W/O Fluid Placebo	a	a	a	a	a	a
W/O Blend Placebo	a	a	b	b	a	a
W/O Elastomer Placebo	a	a	a	b	a	a

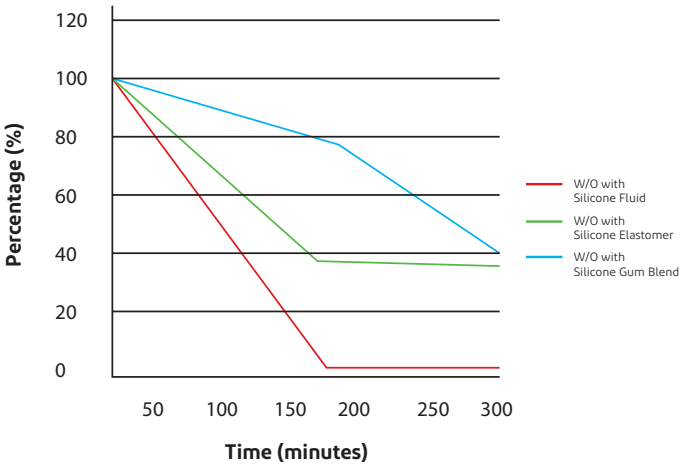
Note: For each parameter, the use of the same letter indicates that the related test samples do not show any significant difference (95% similarity).

Figure 10. Sensory evaluation summary graph for the W/O placebo emulsions

C) Substantivity versus time

With reference to Figure 11, the nature of the silicone polymer in the W/O emulsions had a significant impact on the substantivity versus time. The W/O Blend placebo emulsion showed a good substantivity, both short term and medium terms, as 75 percent of silicone remained on the skin after 3 hours and 40 percent after five hours. The medium term substantivity (5 hours) of the W/O Elastomer placebo was similar to the W/O Blend placebo one despite a quick loss of silicone matter within the first 3 hours, which then stabilized around 35 percent after three hours leading to more than 30% after 5 hours. W/O Fluid placebo formulation showed a poor substantivity as less than 6% of silicone remained on the skin after three and five hours.

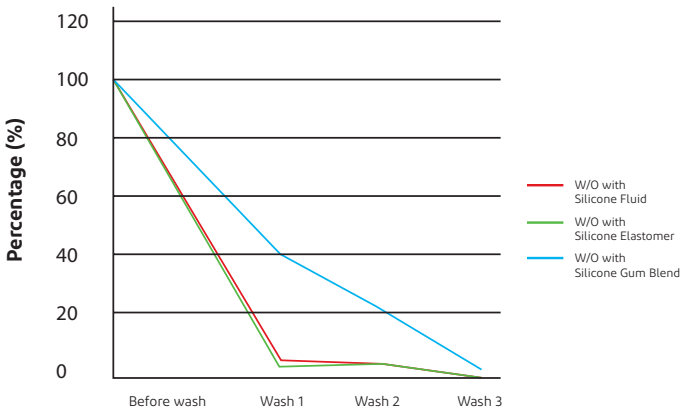
Figure 11. Substantivity versus time of the W/O placebo emulsions



D) Substantivity versus washes

As shown in Figure 12, the nature of the silicone polymer in the W/O Emulsions had also impacted the wash-off resistance of the film resulting from the application of the W/O placebo emulsions. The W/O blend placebo presented a medium wash-off resistance: 40 percent of silicone remained on the skin after one wash but none after three washes. Both W/O Fluid and Elastomer placebo did not show any wash off resistance as no silicone was observed even after the first wash.

Figure 12. Wash-off resistance of the W/O placebo emulsions



Conclusions

The versatility of the silicone chemistry in terms of functionalities and characteristics, translated into an easy to use excipient tool box for topical applications, may offers a wide range of formulation options to load, stabilize and release various drugs for dermatological and local treatments as demonstrated by the corticosteroid containing W/O emulsions evaluated in this article. Optimizing the efficiency of the drug delivery and the behavior of the formulation on skin would certainly lead to better perceived efficacy by the patient associated with a more pleasant sensory feel. Such performance benefits may potentially increase the patient compliance to the treatment requirements. DuPont™ Liveo™ offers a wide range of innovative silicone materials for formulators to consider when developing new drug products for delivering corticosteroids and other drugs delivered topically.

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Form Number: 001-20489-CDP0820