DuPont™ Liveo™ silicone technologies for healthcare demonstrate drug delivery efficiency, robustness and flexibility in topical pain relief formulations

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Introduction

In both personal care and pharmaceutical applications, the use of silicone materials in topically applied products is well-established. Silicones' unique properties – including hydrophobicity, film-forming and inertness – may be imparted into formulated products. Each physical form of silicone materials – whether liquid, solid or crosslinked swollen gel – offers unique performance characteristics and contributes to formulation design and development. Out of several formulation dosage forms commonly applied on the skin, semisolid formulation dosages generally are most common.

Depending on the semisolid formulation's end use, aesthetic characteristics like spreadability, non-greasiness and substantivity gain significance; however, when formulations are prepared with active pharmaceutical ingredients (APIs) or drugs, the efficacy of drug delivery becomes the matter of prime importance. This is due to the therapeutic indication for which the formulation is developed. At the same time, aesthetic characteristics may impact drug outcomes by contributing to improved patient compliance. This often is dictated by the indication or indications for which the formulation is made.

Out of the many indications for which topical formulations are utilized, pain has its own characteristics, complications and formulation requirements to alleviate patients' pain. Most commonly, semisolid products are intended for local pain relief and are applied on a non-compromised skin surface. Topical analgesic drugs and non-steroidal anti-inflammatory drugs (NSAIDs) are two categories of drugs available for pain relief. Lidocaine (LDC) is a topical analgesic and is primarily indicated for acute pain conditions like back/neck/shoulder pain, in which the drug provides therapeutic benefit by locally acting on the surface of the skin. NSAIDs containing topical products may be indicated for chronic conditions such as arthritis pain, where the drug can provide localized relief while avoiding the side effects associated with oral delivery.

Irrespective of the type of drug, it is important to note that the formulation excipients play a key role in drug release to the skin and/or permeation through skin for the intended therapeutic benefit.

In this regard, this report showcases several formulations made using silicone technologies – and their effectiveness in support of drug release or drug permeation. These are compared with commercially available benchmark products in parallel. Model drugs of Lidocaine (LDC), Diclofenac Sodium (DCF) and Ibuprofen (IBP) were used in the formulations. The concentrations of the drugs in the silicone test formulations were the same as the corresponding commercial benchmarks. It also is to be noted that some of the silicone technologies used are not single ingredients; rather, they are a blend of at least two ingredients or a blend by synthesis and manufacturing. This is to illustrate the benefits of blends relative to formulation performance, as well as DuPont's intention to provide blends of multiple technologies to support formulation development.

Formulations with NSAIDs

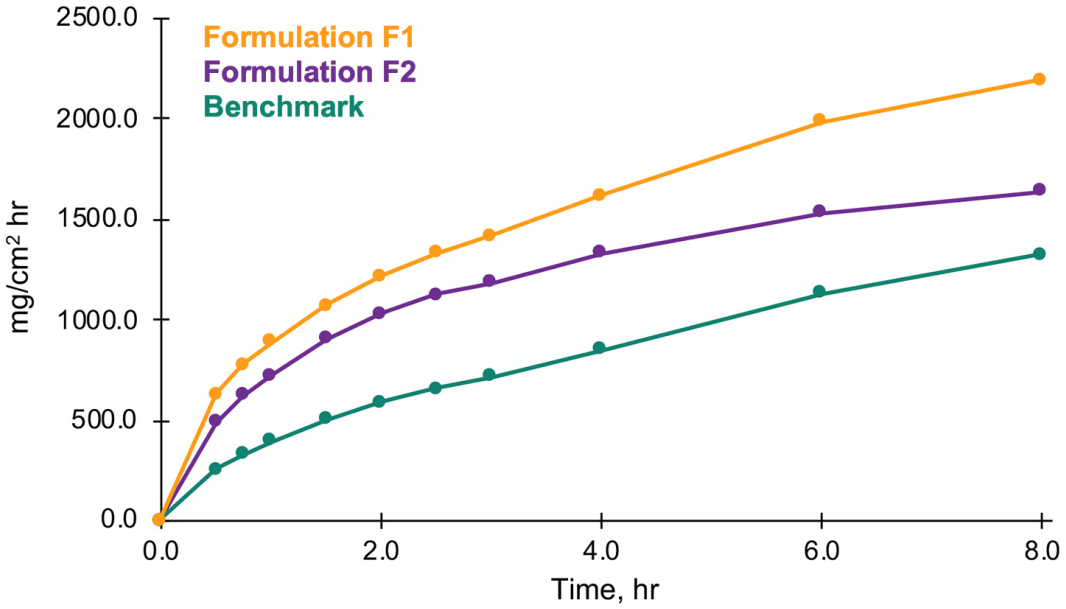
Case #1: Release of Diclofenac Sodium (DCF)

Two formulations (**F1** and **F2**; Table 1) made of different silicone technologies were prepared and evaluated for the release of DCF (through synthetic membrane) from the formulations and compared to a commercial benchmark. Throughout the 8-hour study, the release of DCF observed was higher than that of the commercial benchmark (Figure 1).

Table 1. Composition of silicone-based formulations F1 and F2.

Ingredient	F1	F2
	% w/w	% w/w
DCF	1.0	1.0
Liveo™ Q7-9120 Silicone Fluid, 12500 cSt	17.3	–
Propylene Glycol	6.0	20.0
Isopropyl Alcohol	10.0	10.0
Polysorbate 80	1.0	1.5
Liveo™ ST-Elastomer 10	–	10.0
Dimethicone, 5 cSt	–	10.0
Hydroxypropylmethylcellulose	1.7	1.4
Water	q.s.	q.s.
Benzyl Alcohol	1.0	1.0

Figure 1. DCF release from silicone formulations F1 and F2 versus a benchmark, which is a gel containing 1.16% Diclofenac Diethylamine (equivalent to 1% DCF).



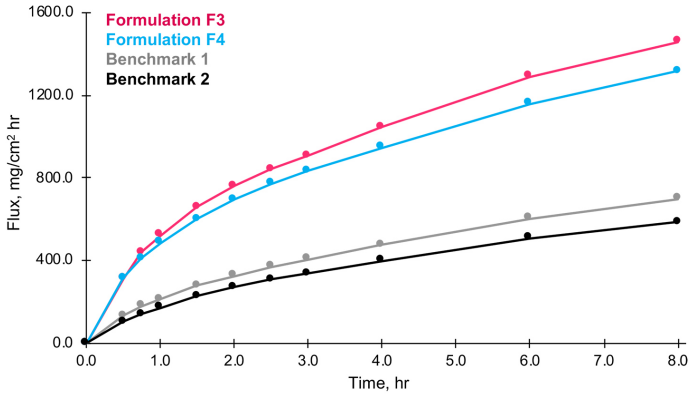
Case #2: Release of DCF amidst other actives

Two formulations (**F3** and **F4**; Table 2) were made using the same silicone technologies as in **F1** and **F2**, but with different overall formulation compositions. In addition to DCF, **F3** and **F4** were made with three other active ingredients – Menthol, Linseed Oil and Methyl Salicylate – and compared with two benchmarks that also contain multiple active ingredients. Once again, throughout the 8-hour study duration, silicone-based formulations **F3** and **F4** demonstrated higher release of DCF than the benchmarks (Figure 2), suggesting that the presence of these additional actives are not deleteriously impacting the release of DCF.

Table 2. Composition of silicone-based formulations F3 and F4.

Ingredient	F3	F4
	% w/w	% w/w
DCF	1.0	1.0
Menthol	5.0	5.0
Linseed Oil	3.0	3.0
Methyl Salicylate	10.0	10.0
Propylene Glycol	10.0	10.0
Isopropyl Alcohol	5.0	5.0
Oleyl Alcohol	1.5	1.5
Liveo™ ST-Elastomer 10	5.0	–
Liveo™ Q7-9120 Silicone Fluid, 12,500 cSt	–	5.0
Dimethicone, 5 cSt	5.0	5.0
Hydroxypropylmethylcellulose	1.4	1.4
Water	q.s.	q.s.
Benzyl Alcohol	1.0	1.0

Figure 2. DCF release from silicone formulations F3 and F4 versus two benchmarks. Benchmark 1 is a gel containing 1.16% Diclofenac Diethylamine (equivalent to 1% DCF), 10% Methyl Salicylate, 5% Menthol and 3% Linseed Oil. Benchmark 2 is a gel containing 1% DCF, 15% Methyl Salicylate and 5% Menthol.



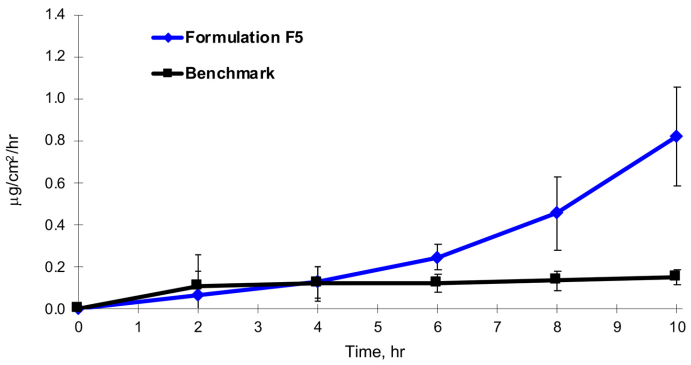
Case #3: Permeation of DCF

A hydroalcoholic formulation, **F5**, was made using only ingredients that are listed in the U.S. Food and Drug Administration Inactive Ingredients Database (FDA-IID), including silicone fluid technologies. This formulation was evaluated against a commercial benchmark for the permeation of DCF. The silicone formulation **F5** delivered 2.7x higher than the benchmark at the end of the 10-hour study period. See Table 3 for formulation composition and Figure 3 for flux profiles.

Table 3. Composition of silicone-based formulation F5.

Ingredient	F5
	% w/w
DCF	1.0
Liveo™ Q7-9120 Silicone Fluid, 12,500 cSt	17.0
Liveo™ Q7-9120 Silicone Fluid, 20 cSt	3.0
Hydroxypropylmethylcellulose	1.7
Water	20.0
Propylene Glycol	10.0
Oleyl Alcohol	1.0
Isopropyl Alcohol	44.3
Benzyl Alcohol	1.0

Figure 3. DCF permeation profile from silicone formulation F5 versus a benchmark. Experiment was carried out using cadaver skin epidermis. Benchmark was a hydroalcoholic gel containing 1% DCF.



Case #4: Permeation of Ibuprofen (IBP)

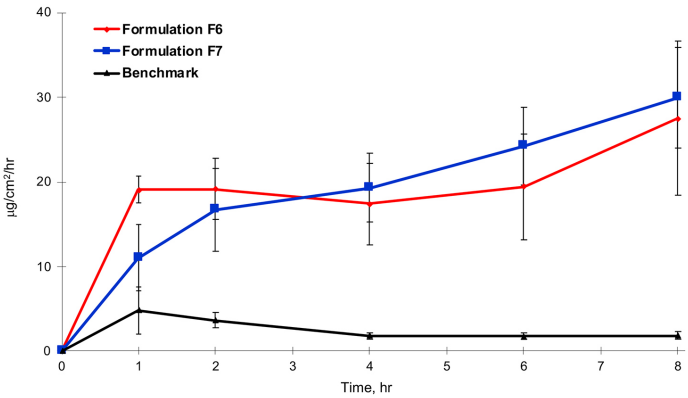
Two hydroalcoholic formulations, **F6** and **F7**, were made and evaluated against a benchmark for the permeation of IBP. Formulation **F6** contains only FDA-IID-listed ingredients. The DuPont™ Liveo™ ST-Elastomer 10 in **F7** is not FDA-IID listed but has drug master file (DMF) support from DuPont. The silicone formulations, both **F6** and **F7**, delivered about 10x higher IBP than the benchmark at the end of the 8-hour study period. See Table 4 for formulation composition and Figure 4 for flux profiles.

Table 4. Composition of silicone-based formulations F6 and F7.

Ingredient	F6	F7
	% w/w	% w/w
IBP	5.0	5.0
Dimethicone, 30,000 cSt	20.0	–
Liveo™ ST-Elastomer 10[(1)]	–	20.0
Hydroxypropylmethylcellulose	2.0	2.0
Water	30.0	30.0
Propylene Glycol	15.0	15.0
Oleyl Alcohol	1.0	1.0
Isopropyl Alcohol	27.0	27.0

[(1)]New low-cyclic-siloxanes-compliant version of Liveo™ ST-Elastomer 10 now available.

Figure 4. IBP permeation profile from silicone formulations F6 and F7 versus a benchmark. Experiment was carried out using cadaver skin epidermis. Benchmark was a hydroalcoholic gel containing 5% IBP.



Formulations with topical analgesic drug Lidocaine

Lidocaine (LDC) is one of the most commonly used over-the-counter (OTC) medications at different dosage forms for topical pain relief. Semisolid topical formulations often are emulsion-based creams. Hence, emulsion-based formulations were prepared and studied when evaluating DuPont™ Liveo™ silicone technologies in the formulations.

Case #1: Release of Lidocaine (LDC)

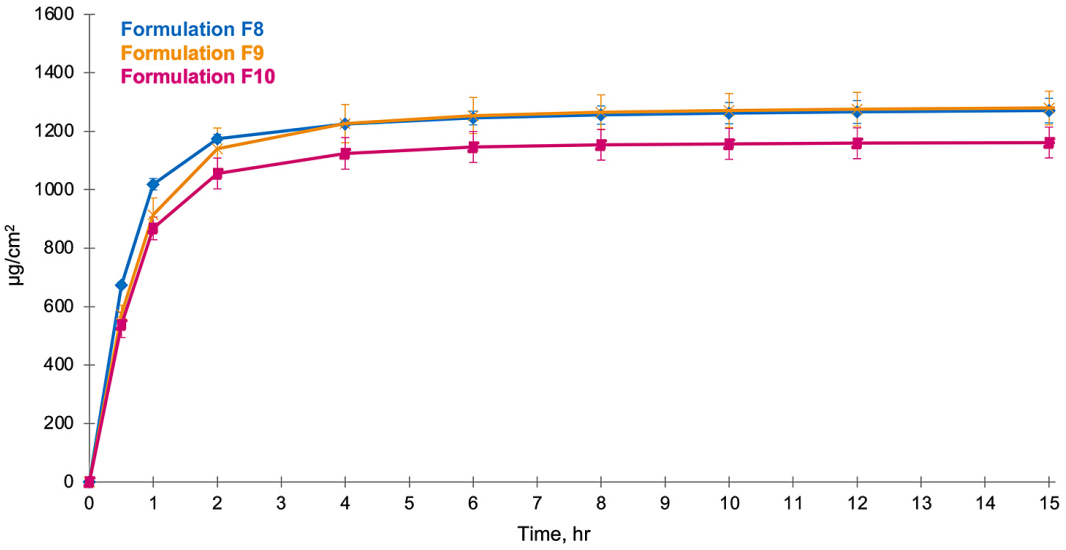
Three different DuPont™ Liveo™ silicone technologies for healthcare were used to make emulsions with similar compositions; the only differences between the formulations were the different silicone technologies. The LDC release results were comparable, regardless of the form of silicone used in the respective emulsions. See Table 5 for formulation compositions and Figure 5 for release profiles.

Table 5. Composition of silicone-based formulations F8, F9 and F10.

Ingredient	F8[(2)] % w/w	F9 % w/w	F10 % w/w
Liveo™ Q7-9120 Silicone Fluid, 20 cSt	5.0	–	–
Liveo™ ST-Elastomer 10	–	5.0	–
Liveo™ Dimethiconol Blend 20	–	–	5.0
Lauryl PEG/PPG 18/18 Methicone	2.0	2.0	2.0
Isopropyl Myristate (IPM)	17.5	17.5	17.5
Water	72.0	72.0	72.0
Sodium Chloride	1.0	1.0	1.0
LDC	2.5	2.5	2.5

[(2)]***F8*** *becomes* ***F8a*** *when ODD is used in place of IPM.*

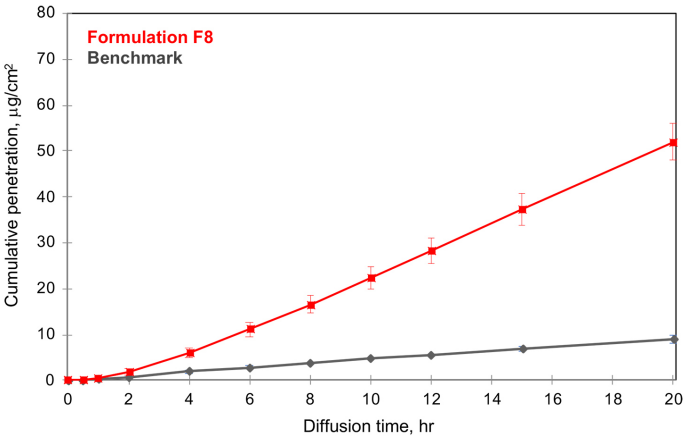
Figure 5. LDC release profile from silicone formulations F8, F9 and F10. Release studies carried out using polyether sulfone membrane.



Case #2: Penetration of Lidocaine versus benchmarks

Having observed similar release behavior among three formulations using different DuPont™ Liveo™ silicone technologies for healthcare, it was decided to take one formulation, **F8**, and compare it with a commercial benchmark product in terms of penetration of LDC. In the penetration studies of LDC in Figure 6 and Figure 7, piglet epidermis was used as the permeation membrane. The LDC permeability profile for **F8** is in Figure 6.

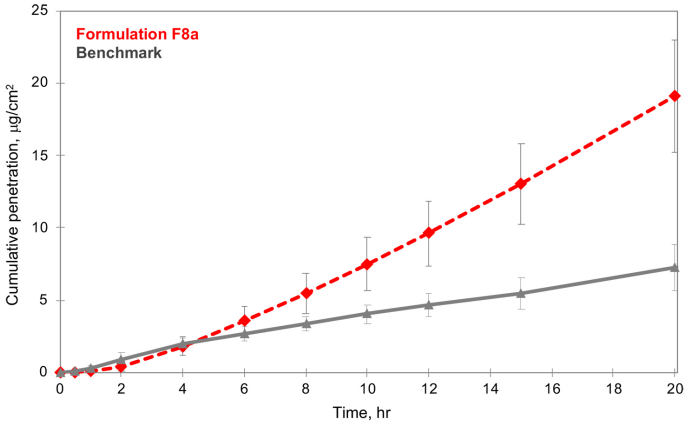
Figure 6. LDC permeation profile from silicone formulation F8 versus a benchmark, which was a cream containing 2.5% LDC and 2.5% Prilocaine. Piglet skin from the same donor was used in experiments corresponding to the data presented in Figures 6 and 7.



The penetration of LDC from **F8** was consistently higher than the benchmark throughout the 20-hour study duration.

To investigate the robustness of the silicone emulsion in delivering LDC when different co-solvent/penetration enhancer was used in the formulation, **F8** was made again, but with Octadodecanol (ODD) instead of Isopropyl Myristate (IPM) and labeled as **F8a**. The efficiency of **F8a** in delivering LDC was evaluated via permeability study against the same benchmark. Figure 7 shows the permeability profile, which clearly indicates **F8a**'s efficiency in delivering LDC compared to the benchmark, as was true for **F8**.

Figure 7. LDC permeation profile from silicone formulation F8a versus a benchmark, which is a cream containing 2.5% LDC and 2.5% Prilocaine. F8a is the same as F8, except that ODD was used in F8a instead of IPM. Piglet skin from the same donor was used in experiments corresponding to the data presented in Figures 6 and 7.



Case #3: Penetration of Lidocaine (LDC)

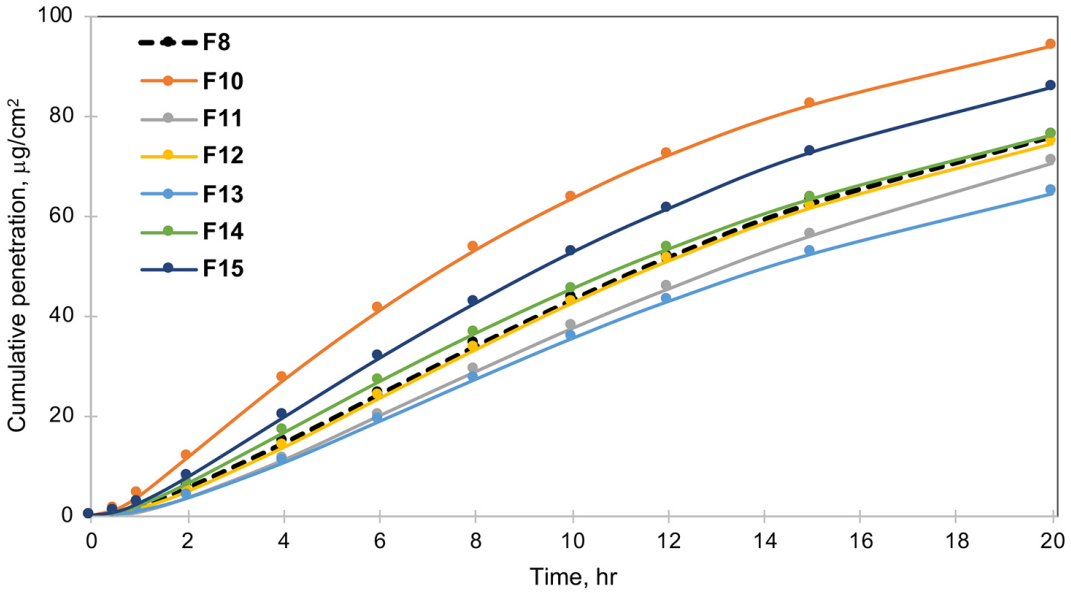
Six different silicone technologies were used to make formulations with compositions very similar to **F8**, and the penetration of LDC was compared against **F8**. Because **F8** and **F8a** already demonstrated superior LDC delivery against the commercial benchmark, **F8** was used as an internal control to evaluate the LDC delivery efficiency of the new formulations, which are made of different silicone technologies.

Table 6. Composition of silicone-based formulations F11 to F15.

Ingredient	F11 to F15 % w/w
Silicone technology used in formulation[3]	5.0
Lauryl PEG/PPG 18/18 Methicone	2.0
Isopropyl Myristate (IPM)	17.5
Water	72.0
Sodium Chloride	1.0
LDC	2.5

[3]***F11*** *uses Dimethiconol (and) Dimethicone (INCI name), a blend of high-molecular-weight silicone gum in non-volatile silicone fluid.* ***F12*** *uses Trimethylsiloxysilicate (and) Dimethicone (INCI name), a blend of silicone resin in non-volatile silicone fluid.* ***F13*** *uses a silicone adhesive that is a blend of solid silicone pressure sensitive adhesive (PSA) in a non-volatile silicone fluid.* ***F14*** *uses Dimethiconol (and) Dimethicone (INCI name), a blend of high-molecular-weight silicone gum in non-volatile silicone fluid and Trimethyl-siloxysilicate (and) Dimethicone (INCI name), a blend of silicone resin in non-volatile silicone fluid.* ***F15*** *uses DuPont™ Liveo™ Q7-9120 Silicone Fluid, 1000 cSt (INCI name: Dimethicone Fluid).*

Figure 8. LDC permeation profiles from silicone formulations F10 to F15 versus internal control F8. Multiple permeability experiments were carried out using piglet skin from different donors. In each permeability experiment, F8 and a formulation containing silicone were evaluated. Results from several permeability experiments were combined and represented here after applying normalization for better comparison. Average data value from six replicates used in the experiments for each formulation are used. Data variability exists due to biological membrane use; however, standard deviation was avoided here for clarity.



The LDC penetration of all the formulations, **F10** to **F15**, with different silicone technologies was comparable to or better than that observed for **F8**. This indicates that irrespective of the differences in the unique characteristics associated with each silicone technology (fluid/gum blend/resin blend/adhesive), the formulations are robust enough to provide a similar drug delivery profile as the internal benchmark (**F8**). It is emphasized that **F8** is an internal benchmark that already demonstrated enhanced delivery of LDC against a commercial benchmark.

This provides important benefits to formulators in such a way that a specific characteristic can be achieved without compromising drug delivery performance. For example, the formulation made using silicone fluids (20 cSt or 1000 cSt) provides good spreadability but less substantivity on the skin surface. If substantivity is desired, the formulation can be made using silicone resin or gum. Thus, these technologies offer formulation flexibility without compromising drug delivery.

All the formulations, **F8** to **F15**, also were evaluated for substantivity (rub-off resistance testing), sensory (human volunteers) and occlusivity (Payne cup test methodology). All formulations showed similar water vapor permeability (Payne cup method) and an A-rating sensory profile. The substantivity order, from high to low, is **F13**>**F14**>**F12**>**F11**=**F15**>**F8**.

Conclusion

Topical semisolid formulations made using several silicone technologies demonstrated efficient drug delivery using three model drugs: Lidocaine, (LDC, a local anesthetic), Diclofenac Sodium (DCF, an NSAID) and Ibuprofen (IBP, an NSAID). Case studies described in this paper confirmed the performance benefits associated with silicone-based formulations – including sensory, substantivity and occlusivity – without compromising drug delivery efficiency, thereby providing options to formulators.

Experiment details

Materials

DuPont™ Liveo™ Q7-9120 Silicone Fluid, 20, 1000 or 12,500 cSt (INCI name: Dimethicone) are high-purity non-volatile silicone fluids. **DuPont™ Liveo™ ST-Elastomer 10** (INCI name: Cyclopentasiloxane [and] Dimethicone Crosspolymer) is a crosslinked polymer network swollen in volatile silicone fluid; DuPont now offers sustainable, low-cyclic-siloxanes-compliant versions of DuPont™ Liveo™ ST-Elastomer 10. **DuPont™ Liveo™ Dimethiconol Blend 20** (INCI name: Dimethicone [and] Dimethiconol) is a high-molecular-weight silicone gum dispersed in non-volatile silicone fluid. Trimethylsiloxysilicate (INCI name) is a silicone resin. Silicone adhesive is a silicone pressure sensitive adhesive (PSA) in a non-volatile silicone fluid. Trimethylsiloxysilicate and Dimethicone (INCI name) is a blend of silicone resin in non-volatile silicone fluid. Dimethiconol and Dimethicone (INCI name) is a blend of high molecular weight silicone gum in non-volatile silicone fluid. The aforementioned materials were obtained in-house.

The other ingredients used in the formulations were obtained either from chemical suppliers, such as Fisher Scientific, or from the respective manufacturers/distributors/suppliers.

DuPont™ Liveo™ silicone technologies for healthcare were used alone and/or combined with other technologies to demonstrate performance benefits to the formulations. Due to the dynamic supply chain situation, it is recommended to contact DuPont™ Liveo™ Healthcare Solutions to determine current availability of these technologies for any evaluation and/or commercial purpose. If a particular technology is not offered, DuPont™ Liveo™ experts can assist with alternatives or recommendations.

Methods

Both release and penetration studies were carried out using a manual Franz diffusion cell console unit at 32°C. Synthetic membranes (0.45 μm cellulose nitro or polyether sulfone) were used for release studies. Heat-separated cadaver epidermis or dermatomed (~500 μm) piglet skin was used for permeability studies. An ultraperformance liquid chromatography system was utilized for method development, as well as for assaying respective drugs. Sensory and substantivity evaluations were carried out with the help of human volunteers. Occlusivity was determined using the Payne cup method.

For questions about this paper

Please email Hyder Aliyar at **hyder.aliyar@dupont.com**.

About DuPont™ Liveo™ Healthcare Solutions

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