(Trans)dermal delivery of lidocaine from silicone topical excipients across pig skin

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PURPOSE

The use of silicone excipients for topical drug delivery has been limited to enhancing the sensory performance of the formulation.

The potential of silicones to promote the release and delivery of drugs across the skin has only been well-established in the area of transdermal administration, in which silicone pressure-sensitive adhesives are commonly used[1].

In the field of topical delivery, the current knowledge of formulating effectively with silicones to enhance drug delivery from the formulation is very limited.

The objective of the present investigation was to assess the impact of several silicone topical excipients on the delivery of the model active lidocaine across pig skin *in vitro*.

MATERIAL & METHODS

Basic topical formulations, e.g. spray, liquid, ointment and hydrogels, containing 2.5% lidocaine were formulated using several Dow Corning® silicone excipients:

Generic name	Abbreviation	Commercial name
Cyclopentasiloxane	D5	Dow Corning® ST-Cyclomethicone 5-NF
Polydimethylsiloxane 5cSt	PDMS 5cSt	Xiameter® PMX-200 5cSt
Dimethicone crosspolymer in cyclopentasiloxane	9040	Dow Corning® ST- Elastomer 10
Dimethicone crosspolymer in polydimethylsilxoxane 5cSt	9041	Dow Corning® 9041 Silicone Elastomer Blend
Dimethiconol in cyclopenta-siloxane (gum blend)	1501	Dow Corning® 1501 Fluid
Dimethiconol in polydimethyl-silxoxane 5cSt (gum blend)	1503	Dow Corning® 1503 Fluid
Hydroxy-terminated dimethicone fluid	D40	Dow Corning® ST-Dimethiconol 40

White petrolatum and Carbopol 974® were used as base for a occlusive ointments or hydrogels, respectively.

Where appropriate, organic solvents such as isopropylmyristate (IPM) or diethyleneglycol-monoethylether (Transcutol®) were used to compatibilise the lidocaine base with the different silicone and hydrogel matrices.

The basic formulations were composed as follows:

Component	All formulas except hydrogels	Hydrogels
Lidocaine	2.5%	2.5%
IPM	17.5%	-
Silicone base or silicone/petrolatum blend	80.0%	-
Transcutol® or D40	-	10.0%
D5 or PDMS 5 cSt	-	0 – 5.0%
Carbopol® gel	-	82.5 – 87.5%

The delivery of lidocaine across dermatomed pig skin *in vitro* (n=3) was studied at 32°C using a static Franz cell set-up with a penetration surface of 1.77 cm², and sampled hourly via a Logan 912 autosampler system. PBS pH 7.4 served as receptor fluid.

EMLA® cream (2.5% lidocaine and 2.5% prilocaine in an eutectic mixture) served as commercial comparison. For reasons of simplicity, the benefit of enhancing delivery of lidocaine via melting point depression, e.g. in the eutectic mixture[2], was not exploited in the formulation approach with silicones.

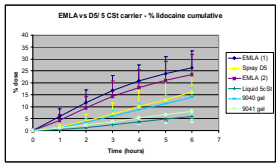
To correct for slight differences in the concentration of the formulations and amounts applied in each donor chamber (40-70 mg of formulation), data are expressed as % lidocaine of the initially applied dose.

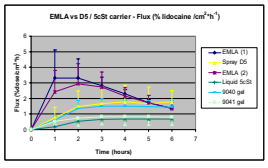
RESULTS & DISCUSSION

1. "Spray" / liquid formulations ("D5" and "PDMS 5cSt")

D5 was a superior solvent compared to PDMS 5 cSt as carrier for the liquid formulation, leading to higher delivery rates of lidocaine.

For each solvent, i.e. D5 or PDMS 5 cSt, the spray or liquid formulation and the dimethicone crosspolymer formulation (see also point 2) reached identical delivery profiles.





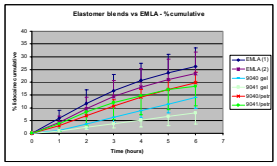
RESULTS & DISCUSSION (cont'd)

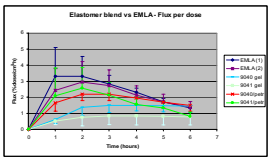
2. Dimethicone crosspolymer formulations ("9040 and "9041")

Under non-occlusive conditions, D5 was a superior solvent compared to PDMS 5 cSt as carrier for the dimethicone crosspolymer formulations.

When formulated as occlusive ointment with petrolatum (70% petrolatum, 30% dimethicone crosspolymer as formulation base), both formulations reached superior delivery rates than using the silicone elastomer alone. The flux profiles of the petrolatum/crosspolymer formulations approached the delivery profiles of EMLA® cream.

Note: These formulations were found metastable in the presence of lidocaine; and, therefore, the penetration enhancement effect was not attributed to occlusivity alone (control experiment not shown).



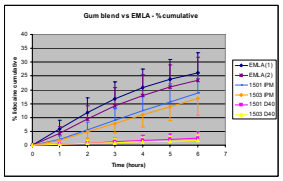


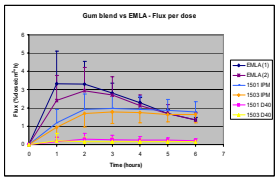
3. Gum blend formulations ('1501" and "1503")

Dimethiconol gum dispersed in either D5 or PDMS 5 cSt showed no difference in delivery profiles.

Lidocaine delivery rates from these formulations were comparable to both the spray and non-occlusive dimethicone crosspolymer formulation containing D5.

Replacing IPM with D40 = hydroxyterminated dimethicone fluid) as dispersing solvent significantly decreases lidocaine delivery across the skin. The same trend was observed in a control experiment, where lidocaine was delivered from IPM or D40 alone (not shown).



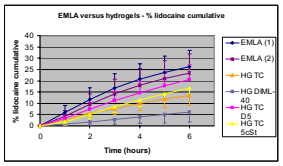


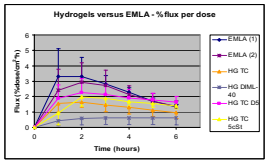
4. Hydrogel formulations ('1501" and "1503")

The hydrogels not containing any silicone showed slightly lower delivery rates than dimethicone crosspolymer blends without petrolatum.

Transcutol® was a superior dispersing solvent compared to D40, although the saturation solubility of lidocaine in Transcutol® was measured two-fold higher than in D40 (not shown).

Adding only 5% D5 or PDMS 5 cSt fluid to the hydrogel formulations with Transcutol® enhanced lidocaine penetration across the skin, in particular when D5 was used.





CONCLUSIONS

The model drug lidocaine can be formulated into a number of formulations containing several silicone topical excipients as formulation base. An organic or hydroxy-functionalised silicone solvent with sufficient polarity was required to compatibilise the drug with the silicone matrix.

The use of different silicone excipients impacted the delivery of lidocaine across the skin. Addition of selected silicone excipients, combined with organic base components such as petrolatum or CarboPol® can therefore be used to achieve sustained or rapid delivery profiles, depending on the desired application.

The solvent used to compatibilise the drug with the silicone matrix strongly influenced lidocaine penetration across the skin. The solubility of the drug in these solvents is one important, but not the only factor, that influences diffusion and partitioning of the drug out of the overall formulation into the skin.

This warrants more systematic investigation of solubility parameters and partitioning coefficients between the drug, the overall silicone formulation and the skin.

The effects of silicone excipients on the delivery of hydrophilic drugs across the skin are yet to be elucidated and are the subject of ongoing investigation.

REFERENCES

1. Peterson TA, Wick SM, Ko C. Design, Development, Manufacturing, and Testing of Transdermal Delivery Systems. In: Ghosh TK, Pfister WR, Yum SI (Eds): *Transdermal and Topical Drug Delivery Systems,* Interpharm Press, Illinois (1997), 249-297
2. Tadicherla S, Berman B. Percutaneous Dermal Drug Delivery for Local Pain Control, *Therapeutics and Clinical Risk Management* 2 (2006), 99–113