SYNERGISING EXCIPIENTS TO BOOST SKIN DELIVERY A CASE STUDY WITH LIDOCAINE HYDROCHLORIDE

E. Dauphin-Chanard; A. Forest; C. Deleglise; M. Ducros; D. Marchaud
GATTEFOSSÉ SAS - Saint-Priest – France - edauphin@gattefosse.com

PURPOSE

Skin delivery remains the most difficult pathway for drug absorption since the *Stratum Corneum* forms an effective barrier against the environment [1]. Different strategies can be adopted to improve the skin penetration of drugs, such as the use of chemical penetration enhancers (CPEs). These should be pharmacologically inert, non-irritant, non-sensitizing, non-phototoxic, and non-comedogenic. The exact mechanism of CPEs is not yet fully elucidated, however 2 groups are commonly acknowledged: **solubilizer**, which increases the gradient of drug diffusion; and **penetration enhancer,** which disturbs the lipid domain of the *Stratum Corneum* [2].

In this study lidocaine hydrochloride (LID HCl), a local anesthetic agent, was used to evaluate the solubilizing performance of each CPE. An *in-vitro* permeation study was conducted using vertical diffusion cells (Franz cells, Strat-M membrane) to compare the diffusion capacity of CPE alone or in mixtures, with the same thermodynamic activity.
This study aimed to identify synergic mixtures of CPEs that enable the solubilization and diffusion/ permeation of LID HCl through the membrane.

MATERIALS & METHODS

Materials
Diethylene glycol monoethyl ether (Transcutol® P, TP), propylene glycol monocaprylate (Capryol™ PGMC, PGMC), propylene glycol monolaurate (Lauroglycol™ FCC, PGML) and polyglyceryl-3 oleate (Plurol® Oleique CC947, PO) are provided by Gattefossé (Saint-Priest, France). Isopropyl myristate (IPM) is supplied by AMI Chimie. Lidocaine hydrochloride (MOEHS, Spain) is used as model drug. All other chemicals used were analytical reagent grade.

Methods
Solubility assessment of Lidocaine HCl
Solubility of LID HCl was determined in CPE (individual or in combination) by adding an excess amount of drug to 10 g of each CPE, stirring for 24 hours (minimum) at 32°C, to allow the pseudo-equilibrium of the mixture. They were then centrifuged at 15000 rpm for 30 minutes. Supernatant samples were diluted with methanol. High Performance Liquid Chromatography (HPLC) was used for evaluation of the drug concentration.

Franz diffusion cells
The *in-vitro* permeation study used vertical diffusion Franz cells (Automatic Microette Vision, from Synersy) with a diffusion area of 1.76 cm^2. Buffer pH 7.4 was used as receptor fluid after sonication and degassing for 30 minutes then maintained at 32 ± 1°C under constant stirring (400 rpm). An infinite dose (1 mL) of mixture was applied to the Strat-M membranes (Merck Millipore) using a micropipette. Diffusion of LID HCl was measured by sampling the receptor phase at t= 30 min, 1h, 3h, 5h, 8h, 12h, 18h and 24h and analysed by HPLC. Replication for each experiment was n = 6.

High-performance Liquid Chromatography (HPLC) analyses
LID HCl concentration was determined by HPLC. A Waters chromatograph Alliance 2695D model coupled with a 2487 model UV detector, equipped with C18-2 (5µm) 150 mm *4.6 mm column (Uptisphere Strategy), was used. Flow rate was 1mL/min and UV detection wavelength 215 nm. The method was validated for linearity, repeatability and specificity.

RESULTS

Solubility assessment of Lidocaine HCl
Solubility performance in various CPEs is presented in table 1.

Table 1: Solubility of Lidocaine HCl in CPEs at 32°C determined by HPLC.

CPE (ratio)	Solubility at 32°C (mg/mL)
Water	796.2 ± 16.7
TP	379.0 ± 14.8
TP/ PGML (7/3)	271.0 ± 8.4
TP/ PGMC (7/3)	253.6 ± 5.6
TP/ PO (7/3)	251.8 ± 1.5
TP/ IPM (7/3)	173.8 ± 3.3
TP/ PGML (5/5)	143.4 ± 9.6
TP/ PGML (3/7)	72.0 ± 0.9
PO	24.9 ± 0.6
PGMC	13.8 ± 0.5
PGML	5.4 ± 0.3
IPM	0.0 ± 0.0

Solubility of LID HCl was found to be higher in hydrophilic vehicles and the rank order was:
Water > TP > PO > PGMC > PGML > IPM.
Combination of fatty acid esters (lipophilic vehicles) with TP decreased LID HCl solubility compared to TP alone.
Since drug must be in molecular state to diffuse through the skin layer, solubility screening is an important and routine step in preformulation protocols. However, the highest drug solubility does not always equate with the best drug diffusion properties. Drug solubility evolves during application when it partitions into the membrane. Diffusion studies are therefore necessary to elucidate which vehicles achieve the right balance between solubility and diffusion.

Diffusion study
LID HCl was added in each individual vehicle or mixtures at 25% of its saturated concentration to compare the diffusion performance with the same thermodynamic activity.

Figure 1: Comparison of diffusion of Lidocaine HCl in single CPE

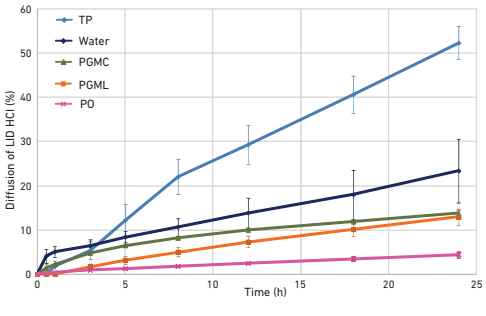


Figure 1 shows that although water provides the highest solubilizing capacity for LID HCl, cumulative diffusion at 24h was below TP with only 23.5% ± 7.1% of the applied dose versus 52.3% ± 3.8 %.

TP shows the best enhancement of drug diffusion with the other vehicles showing no improvement over water. TP has been reported to increase drug diffusion and maintain drug solubility after partition into the membrane [3].
The synergic effect of combining TP with lipophilic CPE to achieve better drug diffusion is well documented. PGML – propylene glycol esters of lauric acid C12 [4] – a penetration enhancer known to affect drug partitioning - was chosen for the first screening.

Figure 2 shows the impact of TP:PGML ratio on LID HCl diffusion. All ratios show a faster drug diffusion during the first hours compared to TP alone. The best ratio is 7 TP to 3 PGML with 31.1 ± 9.5% LID HCl diffusion after 8 hours.

Figure 2: Impact of the ratio TP (solubilizer) to PGML (penetration enhancer)

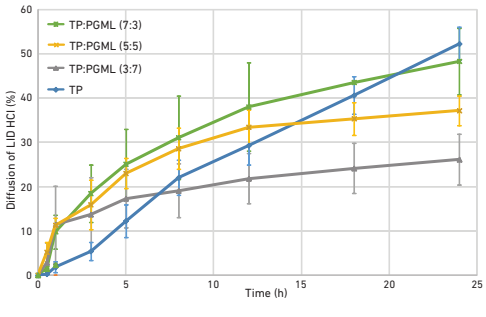
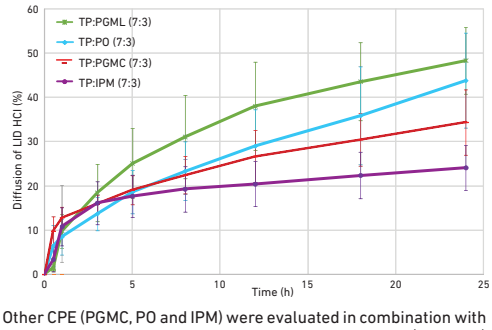


Figure 3: Influence of penetration enhancer in combination with TP (solubilizer)



Other CPE (PGMC, PO and IPM) were evaluated in combination with TP at a ratio of 7 TP:3 CPE. Combination of TP: PGML (7:3, w/w) shows the highest diffusion with 48.3% ± 7.5% of the applied dose after 24 hours (figure 3). PO is a polyglycerol ester of oleic acid (C18:1) reported to increase the fluidity of lipid bilayer of the skin [2]. PGMC is a propylene glycol ester of caprylic acid (C8) [4]. These results corroborate reports that saturated lauric fatty acids (C12) seem to be the optimal chain length for effective penetration enhancement [2].

CONCLUSION

Combining an efficient solubilizer and penetration enhancer achieves a synergic effect which enhances the passive diffusion of LID HCl through the Strat-M membrane in this Franz cell model. Transcutol® P (TP) increased drug solubility in the formulation, whereas Lauroglycol™ FCC (PGML) pushed the drug to partition into the membrane. Lauroglycol™ FCC (PGML) provides better diffusion compared to IPM, Capryol™ PGMC (PGMC) or Plurol® Oleique CC497 (PO) when associated with Transcutol® P (TP) at the fixed ratio of 7:3 (w/w).
We intend to continue this investigation using the excipients and drug formulated in gel and cream, using standard dose of 2% LID HCl (therapeutic level). Diffusion studies will be performed on animal skin to validate the synergic effect of Transcutol® P (TP) combined with Lauroglycol™ FCC (PGML).

REFERENCES

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