



Permeability of anesthetic formulations in Versatile™ cream base

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Local anesthesia

Anesthesia is the temporary induced loss of sensation or awareness while patients do not feel pain during surgical procedures. It can be categorized into three main categories: General anesthesia, Sedation (narcosis) and Local anesthesia.

Local anesthesia outweighs the other two categories because of the immediate recovery, the fewer complications and the fact that patients do not lose consciousness.

There are two main chemical categories of Local Anesthetics:

- Esters (Benzocaine, Tetracaine, Proparacaine e.t.c.)
- Amides (Lidocaine, Prilocaine, Ropivacaine, Bupivacaine e.t.c.)

An In vitro permeability study of benzocaine/lidocaine/tetracaine in semi-solid formulations using experimental design was conducted by

the National and Kapodistrian University of Athens, at the department of Pharmacy.

The study aimed at investigating the following:

- Preparation of anesthetic creams combining Benzocaine, Lidocaine and Tetracaine in Versatile™ cream base, based on the principles of the experimental design
- Determination of the formulations with the best permeability, in Versatile™ cream-base
- Comparison of BLT (20-6-4) combination in cream-base Versatile™ versus PLO, by using artificial membrane Strat-M® and skin
- Stability assessment of the formulations

Individualized topical treatment with accuracy and safety

A topical preparation can be ready in few minutes by simple mixing of the pharmaceutical raw materials in the final dispensing container, following a simple procedure described in the compounding instructions leaflet. This

time-saving solution ensures an individualized dermatological treatment with accuracy and can be considered as beneficial for physicians, pharmacists and patients, while decreasing the possibility of errors.

Fagron Advanced Derma Convenience Pack BLTV



Fagron Advanced Derma Convenience Pack BLTV includes Benzocaine micronized 20%, Lidocaine 6%, Tetracaine 4% in Versatile™, preparation container and compounding instructions.

For more information please contact info@fagron.gr.

Literature review of in vitro permeability study

Mechanism of action

Topical anesthetics reversibly block nerve conduction near their site of administration by targeting free nerve endings in the dermis or mucosa. Specifically, the nerve impulse conduction is blocked by decreasing nerve cell membrane permeability to sodium ions¹.

Generally topical anesthetics (Benzocaine, Lidocaine and Tetracaine) block the initiation and conduction of nerve impulses by decreasing permeability to sodium ions in the neuronal membrane.

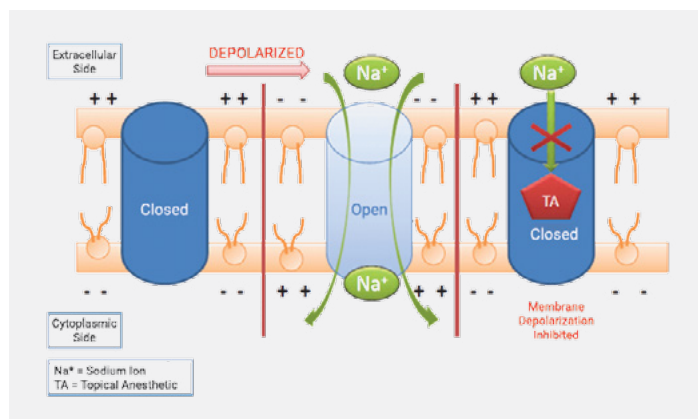
Reversible inhibition of sodium channels:

Free base

Passes through the membrane of the nerve cell.

Ionized form

Attaches to the sodium channel inside the nerve cell (active form).



Eutectic mixture

Eutectic mixture, is a mixture of two or more components, which liquefies at a temperature lower than the melting points of its components and maintains its oily liquid form and not the crystalline solid one. There is an increased permeability of APIs in eutectic mixtures, such as

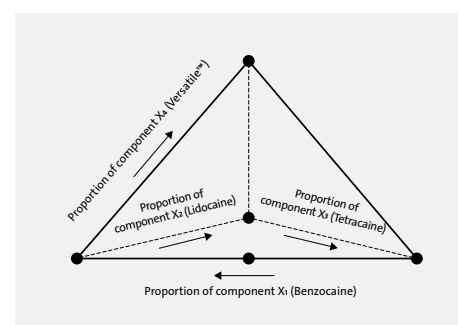
Benzocaine, Lidocaine and Tetracaine at 20-6-4 ratios due to depression of their melting points as the lower the melting point is, the easier it is for a substance to pass through the stratum corneum.

Experimental Design

Mixture and combined design for optimal formulations (different APIs/vehicle concentrations) was applied and the following results regarding permeability were obtained.

Component A: Benzocaine W % w/v	Component B: Lidocaine W % w/v	Component C: Tetracaine W % w/v	Component D: Versatile™ cream base W % w/v
0	15	10	75
0	7	7	86
0	6	4	90
0	6	4	90
0	6	4	90
7	5	10	78
10	15	5	70
10	6	4	80
10	10	10	70
12	0	5	83
13	7	10	70
15	6	4	75
20	6	4	70
20	0	0	80
20	0	4	76

Components	Concentration range
Benzocaine	0-20%
Lidocaine	0-15%
Tetracaine	0-10%
Versatile™	70-90%



Experimental part of in vitro permeability study

Numerical optimization

Three formulations were found to reach the best permeability levels after data processing using Design-Expert® software:

Benzocaine %	Lidocaine %	Tetracaine %	Versatile™ cream-base %	Benzocaine cumulative amount/surface area (µg /cm²)	Lidocaine cumulative amount/surface area (µg /cm²)
17.14	12.86	0	70	47.85	42.29
13.1	6.9	10	70	46.54	34.01
15.33	7.00	7.67	70	43.12	33.23

From all three formulations of experimental design, the best formulation is 17.14-12.86-0 because of the highest permeability results:

For formulation 17.14-12.86-0, permeation experiments were also conducted on Strat-M® membrane

Formulations B-L-T	Cumulative amount permeating the membrane/surface area (µg/cm²)				Flux at 6 h (mg/cm²/hr)
	1 h	SD	2 h	SD	
Benzocaine					
17.14-12.86-0	10.77	4.02	51.07	14.13	0.676
Lidocaine					
17.14-12.86-0	11.26	5.63	58.06	27.52	1.085
Tetracaine					
17.14-12.86-0	0.0	0.0	0.0	0.0	0.0

The formulation 17.14-12.86-0 was also proved one of the best by Strat-M®.

Result

- The best formulation 17.14-12.86-0 was finally decided not to be used because of phase separation
- The second formulation 13.1-6.9-10 and the third formulation 15.33-7.00-7.67 were decided not to be further used since 7% is the maximum percentage of Tetracaine that has been clinically evaluated

Since the three formulations obtained by the numerical optimization were excluded (see the above results), permeability experiments with Strat-M® were conducted in order to find the best combinations.

After evaluating the results of Benzocaine and Lidocaine permeability experiments with Strat-M®*, the following formulations were found to have the highest permeability:

Results of three combinations with the highest permeability of Benzocaine in 2 hours using Strat-M®

Formulations with the highest permeability B-L-T	Cumulative amount permeating the membrane/surface area (µg/cm²)				Flux at 6 h (mg/cm²/hr)
	1 h	SD	2 h	SD	
13-7-10	10.95	4.69	46.54	4.37	0.525
20-6-4 (PLO)	9.78	3.04	40.58	8.14	0.523
20-6-4 (Versatile™)	16.40	3.66	48.81	12.24	0.488

Results of six combinations with the highest permeability of Lidocaine in 2 hours using Strat-M®

Formulations with the highest permeability B-L-T	Cumulative amount permeating the membrane/surface area (µg/cm²)				Flux at 6 h (mg/cm²/hr)
	1 h	SD	2 h	SD	
10-10-10	8.05	0.94	37.95	0.22	0.473
13-7-10	8.70	4.89	37.68	3.86	0.430
20-6-4 (PLO)	6.47	1.88	35.54	6.53	0.488
0-15-10	12.23	0.08	52.33	15.36	0.971
10-15-5	9.42	0.55	40.41	8.48	0.638
20-6-4 (Versatile™)	13.70	2.05	38.00	10.20	0.434

Result

In all the above tables the formulation 20-6-4 (BLT) is proved to be a great combination for permeability during the administration.

* Strat-M® membrane offers good predictability for a variety of active substances, can detect permeability variations for a large number of permeability enhancers and does not show lot-to-lot variability.

Experimental part of in vitro permeability study

Comparison of 20-6-4 in Versatile™ and 20-6-4 in PLO

Versatile™

Versatile™ is a highly elegant hydrophilic vanishing (O/W) cream base that can retain its consistency with a broad range and high concentration of APIs, DCIs and solvents.

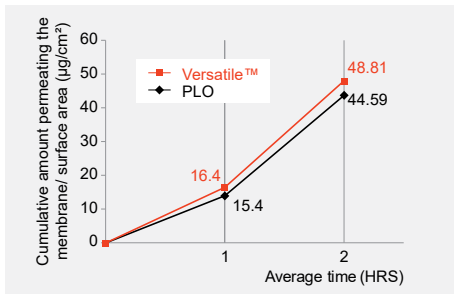
It offers pleasant and soft, non-greasy skin feel for greater patient adherence and is formulated without harmful, obsolete or controversial ingredients, while retaining durability with API concentrations up to 50% and minimizing oxidation. Versatile™ allows for individualized therapy and more accurate dosing.

PLO (Pluronic Lecithin Organogel)

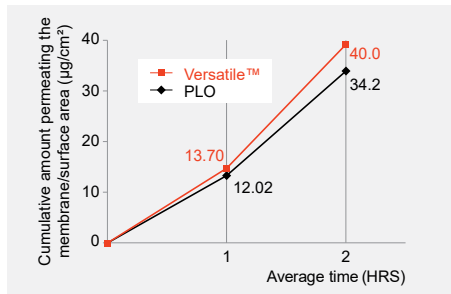
PLO (Pluronic Lecithin Organogel) is used as a dermal drug carrier for hydrophilic and hydrophobic APIs (based on the drug's properties). As the barrier properties of the stratum corneum (SC) cause significant difficulties in the dermal and transdermal delivery of drugs, PLO's lecithin acts as a permeation enhancer.

One part of the study was the comparison of BLT (20-6-4) combination in cream-base Versatile™ and BLT (20-6-4) combination in PLO, by using artificial membrane Strat-M® and skin.

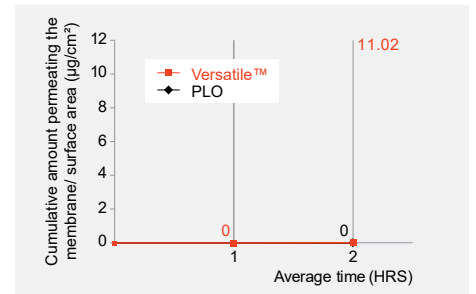
Comparison of results of 20-6-4 in Versatile™ versus 20-6-4 in PLO using Strat-M®



Comparison of Benzocaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using Strat-M®



Comparison of Lidocaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using Strat-M®

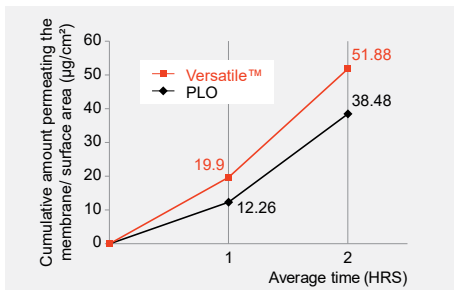


Comparison of Tetracaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using Strat-M®

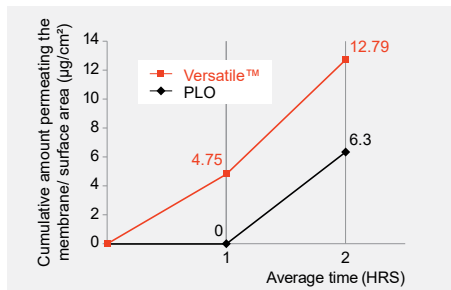
Result

Highest permeability is shown in Versatile™ using Strat-M®.

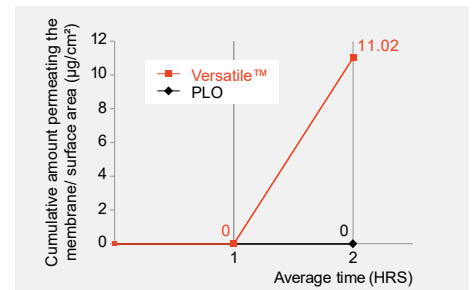
Comparison of results of 20-6-4 in Versatile™ versus 20-6-4 in PLO using skin



Comparison of Benzocaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using skin



Comparison of Lidocaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using skin



Comparison of Tetracaine Permeability in 20-6-4 Versatile™ & 20-6-4 PLO using skin

Result

Highest permeability is also shown in Versatile™ using skin.

Experimental part of in vitro permeability study

Study conclusions

The conclusions drawn from the following study are:

- It is feasible to prepare the anesthetic creams of the experimental design
- Formulation with optimum permeability 17.14-12.86-0 → decided not to be used → phase separation due to stability issues
- Alternatives, 13.1-6.9-10 and 15.33-7.00-7.67 → decided not to be used → further study is required to assess its clinical safety, due to 7% Tetracaine safety limit
- Very good permeability and safety during administration → BLT (20-6-4)
- As a vehicle of BLT, Versatile™ versus PLO is recommended → better permeability to artificial membrane and skin
- Stability: No alterations are macroscopically observed for the creams of the experimental design

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