**OBJ**

LIMITED

Active transdermal drug delivery

OBJ | ETP & eM-patch Test and Evaluation Summary

1 BACKGROUND

OBJ Limited is an Australian drug delivery company focused on the development and commercialization of magnetic enhanced drug delivery technologies for use in the pharmaceutical, dermatology, cosmetic and oral health sectors. The company's business model is work with partner companies in the development of effective transdermal solutions for existing molecules and to commercialize products utilising OBJ's technology platforms.

2 TECHNOLOGIES

OBJ's proprietary technology portfolio include:

ENHANCED TRANSDERMAL POLYMER (ETP) and eM-patch

ETP is a *nonpowered active magnetic materials technology* that uses micro-arrays of magnetic gradients which mobilize drug molecules and alter the barrier effect through a combination of Diamagnetic repulsion and Induce Charge electro Osmosis. The ETP material contains complex intersecting polarity magnetic arrays in a flexible polymer matrix that generate a multiphasic magnetic field capable of enhancing transdermal delivery without disrupting the skin barrier function. It achieves this by utilising diamagnetic repulsion to give energy and directionality during partitioning and diffusion and induced charge electro-osmosis as a means of optimizing delivery pathways. [see Mechanisms of Action, section 5] ETP can be readily incorporated as the patch backing layer in existing drug-in-adhesive and matrix patch technologies to provide a cost-effective and continuous "active patch" delivery solution.

eM-patch is a patch or strip device utilising custom ETP arrays in conjunction with an optimised formation designed to provide finished goods to meet the needs of industry partners or special therapeutic goals.

FIELD-IN-MOTION (FIM)

FIM is a microarray element that when moved as a result of normal consumer scrubbing, brushing and rubbing actions redirects the horizontal energies to enhance drug delivery. FIM can be incorporated into a wide range of devices, brushes, applicators or packaging to product enhanced delivery, reduced time to onset and improved penetration without the use of power. FIM fields are customer designed to the motion, formation and active ingredient to be delivered.

Please Note: OBJ's powered active delivery technology DERMAPORTATION (DP) is not featured in this Summary as the requirement for battery power may make it less relevant to the consumer needs of the Cosmetic, Skincare and Dermatology markets however the extensive studies carried out using Dermaportation can be used to determine the suitability for a drug to magnetic delivery.

3 STUDIES AND EVALUATIONS

Over a period of 5 years, OBJ has studied the suitability of a wide range of therapeutic and cosmetic modules for magnetic enhanced delivery which in turn inform the feasibility of developing products that utilise that technology.

In Vitro Diffusion

The following drugs and ingredients have been evaluated for their suitability to magnetic enhanced delivery in university studies using Franz type diffusion cells and excised human epidermis

- ALA hydrochloride
- β -estradiol
- Caffeine
- Diclofenac diethylammonium salt
- Diclofenac sodium
- Dipeptide Ala-Trp
- Ibuprofen
- Lidocaine Hydrochloride
- Prilocaine Hydrochloride
- Salicylic Acid
- Testosterone
- Tetracaine Hydrochloride

In Vivo

The following drugs were subjected to placebo controlled blinded efficacy studies by independent universities.

- Clostridial related Vaccine (Glanvac)
- Tetracaine (amethocaine)
- Urea (cosmetic)

In Vivo downstream bioeffect

The following drugs and ingredients were evaluated for enhanced bioavailability under the influence of magnetic enhanced delivery through the monitoring of various downstream bioeffects. Optical Coherence Tomography (OCT), Laser Doppler Perfusion, Microrelief, Chromatography, Skin Impedance and Skin Capacitance were amongst the techniques employed and available for evaluations of additional drugs, ingredients and formulations.

- Benzoyl Peroxide
- Carbamide Peroxide
- Clobetasol
- Chondroitin Sulphate
- Glucosamine
- Hyaluronic Acid
- Methyl Nicotinate
- Palmitoyl Pentapeptide-3
- Retinoic Acid
- Terpenol-4-OL
- Triclosan
- Urea

4 ETP AND EM-PATCH EVALUATIONS OF COSMETIC MOLECULES AND COMPOUNDS

In vitro enhanced diffusion evaluations

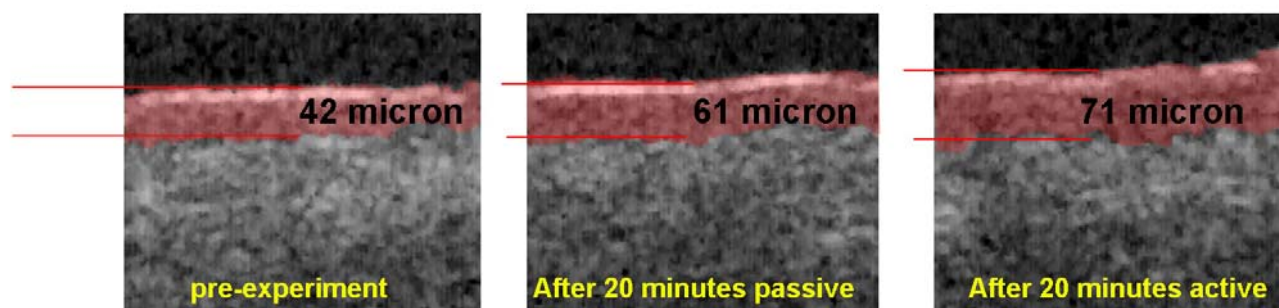
ALA hydrochloride
Caffeine
Dipeptide Ala-Trp
Salicylic Acid

Moisturising Active Ingredients

Urea
Hyaluronic Acid

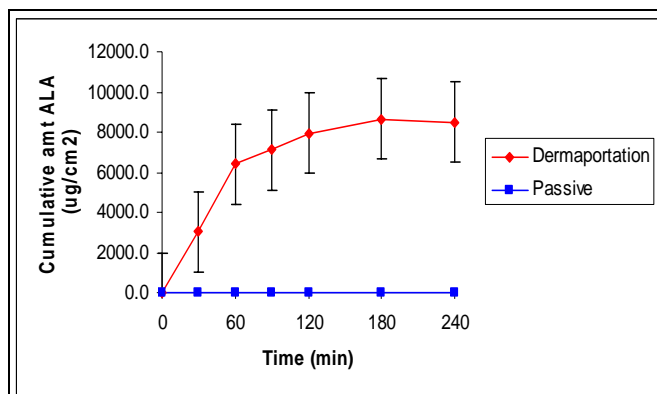
Skin Care Active Ingredients

Retinoic Acid
Palmitoyl Pentapeptide



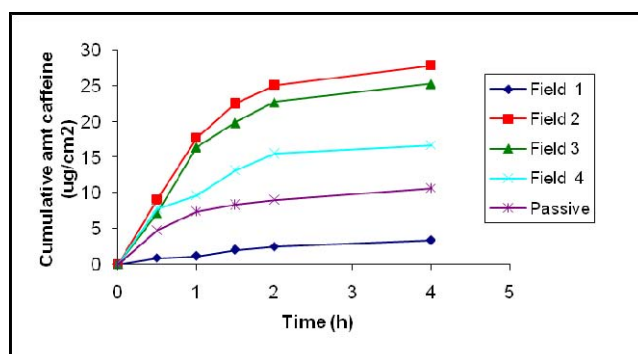
ALA hydrochloride

Overview: ALA solution was applied to the surface of human epidermis for a contact period of up to 4 h. Dermaportation applied continuously from 0 to 4 h was compared to passive diffusion. ALA penetrating the epidermis would diffuse into a receptor fluid of phosphate buffered saline [pH 7.4: PBS]. The receptor fluid was analysed for ALA content by high performance liquid chromatography (HPLC).



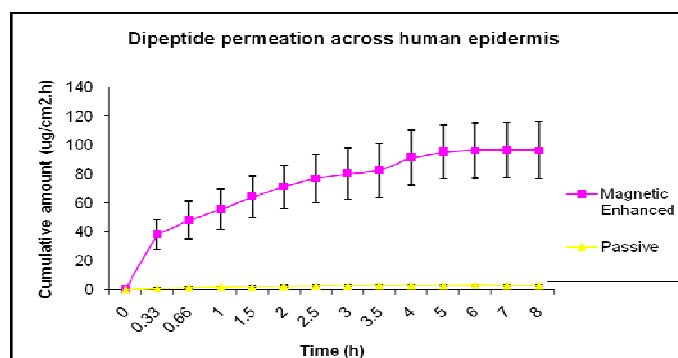
Caffeine

Overview: Caffeine was used as a model drug. Penetration of caffeine across human epidermis in vitro was determined. The influence of various field parameters on skin penetration of caffeine was measured. A range of magnetic energy profiles, as designed by OBJ Ltd, was assessed for their skin penetration enhancement effect.



Dipeptide Ala-Trp

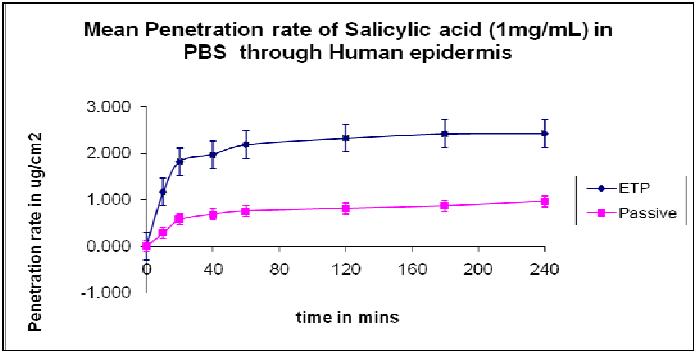
Overview: To evaluate the enhanced delivery of Alanine-Tryptophan (Ala-Trp), a model dipeptide in a phosphate buffered saline solution under the influence of enhanced magnetic delivery by OBJ Limited.



Salicylic Acid

Overview : ETP enhanced delivery of Salicylic acid in PBS

Excised epidermis from 3-4 donors was matched over *three* groups, ensuring an even distribution of donor per group. The three groups were passive, ETP type 1003 was used to enhanced the delivery in diffusion cells containing salicylic acid in PBS in the donor compartment.



Urea

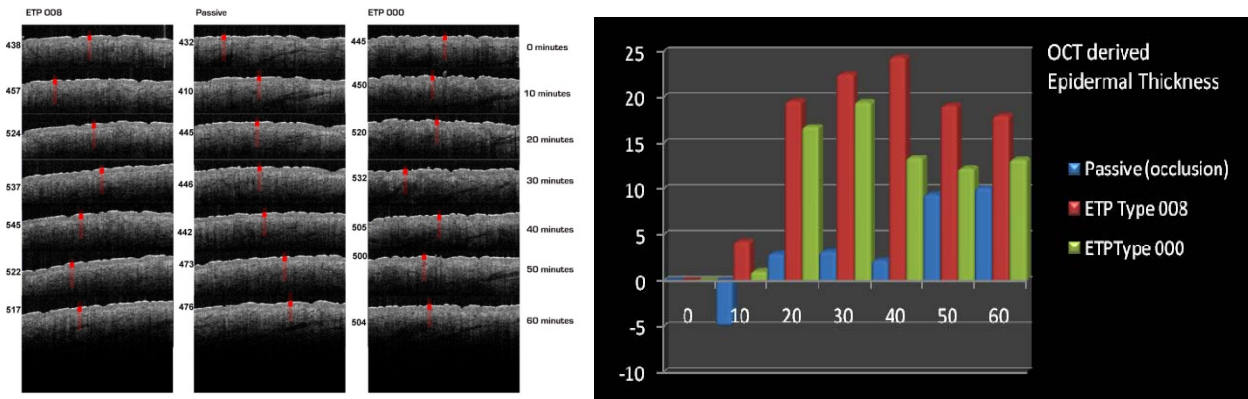
Overview: 5% urea gel was applied to human epidermal membrane in vivo and human skin in vivo.

Application of gel with magnetic film was compared to application with a plastic occlusive film. In vitro epidermal penetration was determined using a Franz-type diffusion system. In vivo permeation was visualized by optical coherence tomography (OCT) of epidermal hydration.

Key findings: The mean cumulative permeation of urea over 2 h for ETP application was $89.54 \pm 7.34 \mu\text{g}/\text{cm}^2$ as compared to $20.83 \pm 2.02 \mu\text{g}/\text{cm}^2$ for passive occluded application (mean \pm sem, n=9/8), representing greater than a 4-fold increase over the 2 h application time period. In the in vivo study the application of 5% urea gel with occlusion increased epidermal thickness by 2.54% and 5.62% after 30 and 60 min respectively. However when urea gel was applied with the magnetic film (ETP008) a 6-fold increase was observed at 30 min, though the increase was less marked at 60 min (2-fold greater).

Conclusions: Administration with a novel magnetic film technology provided enhanced skin penetration of urea and increased epidermal hydration when compared to administration under an occlusive film.

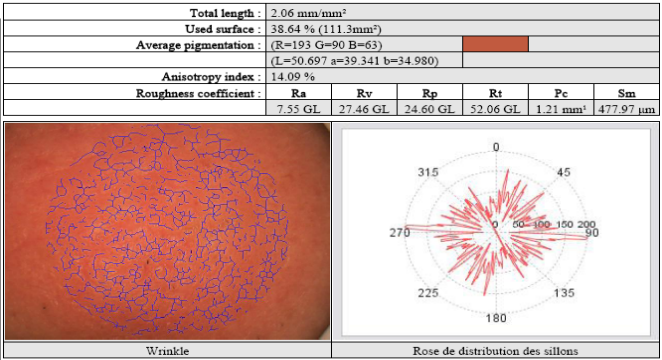
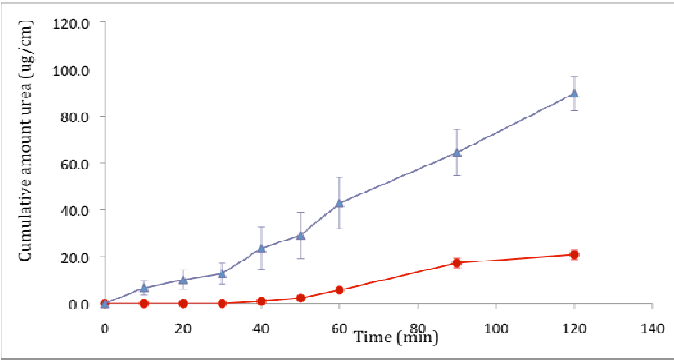
Optical Coherence Tomography (OCT) Evaluations



Invitro Diffusion

Skin Evidence Microrelief

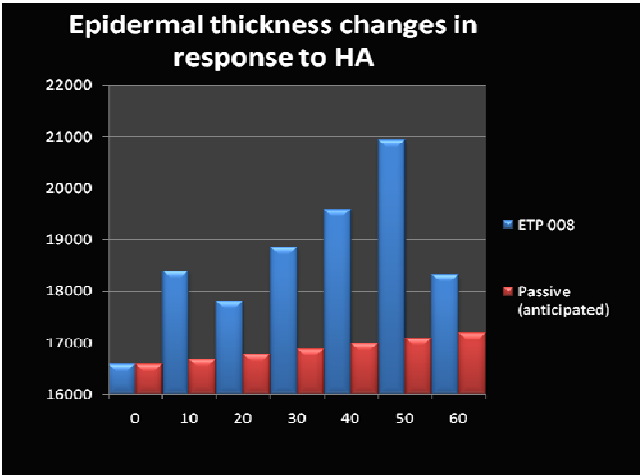




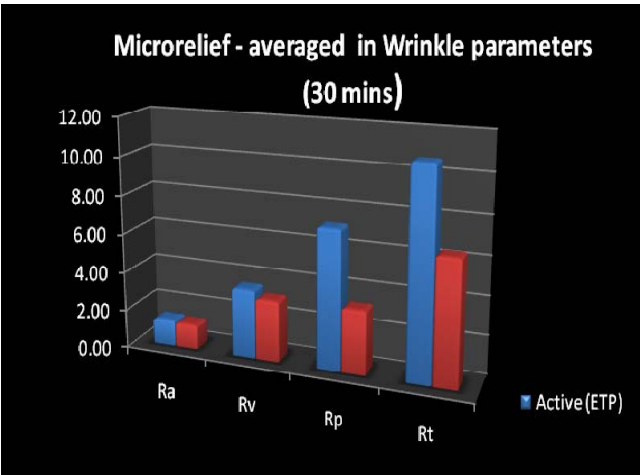
Hyaluronic Acid

Overview: HA, and especially high molecule weight is considered by many to be too large to be introduced successfully into the epidermis via transdermal means. In vitro diffusion studies are of little value due to the potential for degradation and the lack of a suitable assay for MMVHA. To test the suitability of HA to enhanced magnetic delivery a number of studies were undertaken using a range of methodologies.

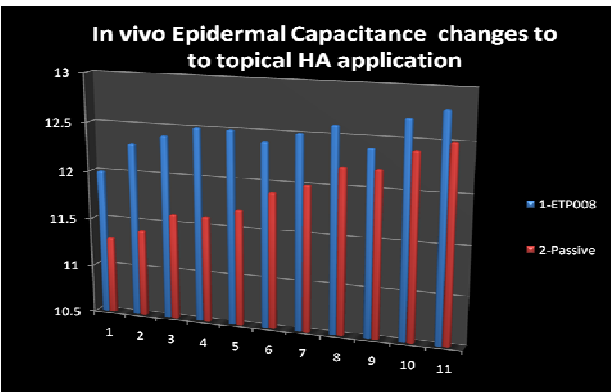
Epidermal Thickness by Optical Coherence Tomography



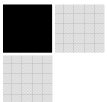
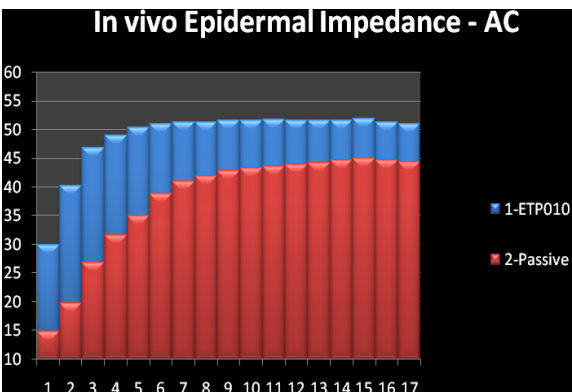
Wrinkle Microrelief



Epidermal Capacitance



AC Epidermal Impedance



Retinoic Acid

Overview: A preliminary in vivo investigation into the feasibility of enhanced delivery of Retinoic Acid. Results suggest some benefit. Requires further investigation.

Passive appliciation

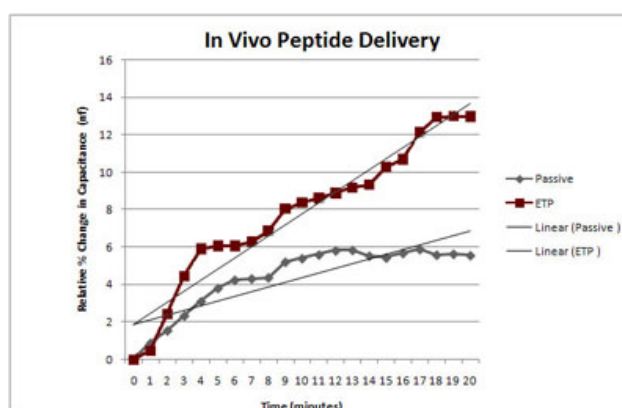


Active ETP applicaiton



Palmitoyl Pentapeptide

The successful topical delivery of peptides is an important area of enhanced drug delivery due to the poor bioavailability through traditional routes. OBJ investigated the delivery of a commercial Palmitoyl Pentapeptide supplied by Cognis using epidermal AC capacitance comparing ETP with Passive occluded delivery.



5 MECHANISMS OF ACTION

Magnetic enhanced drug delivery yet to completely fully characterised. As a result, the precise mechanism of actions can only be proposed in response to the experimental evidence.

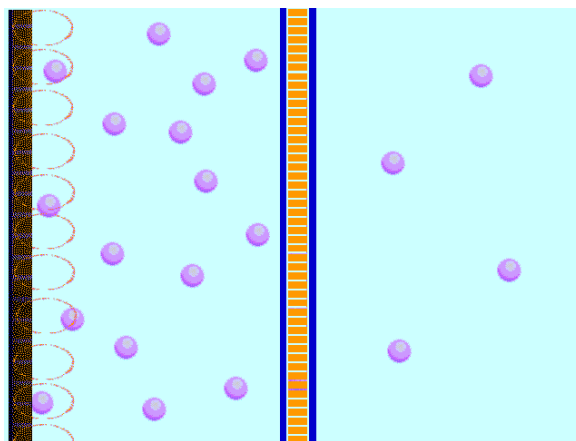
Four mechanism have been identified as contributing to the observed increase in drug delivery across a range of biological barriers.

- *Diamagnetic Repulsion*
- *Follicle, Pore and Shunt Utilisation*
- *Lipid packaging order*
- *Water Binding*

Diamagnetic Repulsion is a repulsive force [opposite of magnet attraction] generated when the rotation behavior of paired electrons in target molecules cause them to be repulsed by the type of magnetic fields using in OBJ's technology. OBJ utilises Diamagnetic Repulsion as a means of providing directionality and energy to Brownian motion and in doing so accelerate diffusion, reduce time to onset, increase penetration and manage partitioning without formulation alterations.

Pore and Shunt Utilisation

The epidermis has numerous pores and shunts, it does not usually participate in drug delivery due to the pores' small diameter and the surface tensions thus created. Induced charge electro-osmosis is used by OBJ to overcome the non-slip barrier effect (surface tensions) which blocks micro-fluidic flow in small diameter follicles, pores and epidermal shunts which are usually closed to passive delivery to make use of more efficient delivery routes. The University of Queensland study image rhodium dye dispersion under passive conditions (left) and under Magnetic enhancement (right) The focusing of available active at the hair follicle can be clearly seen.



Lipid Packing Order

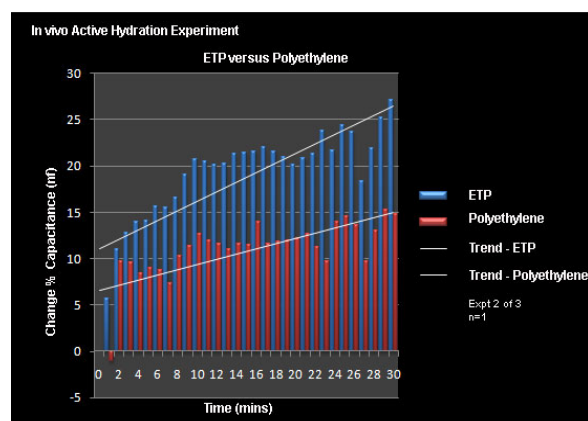
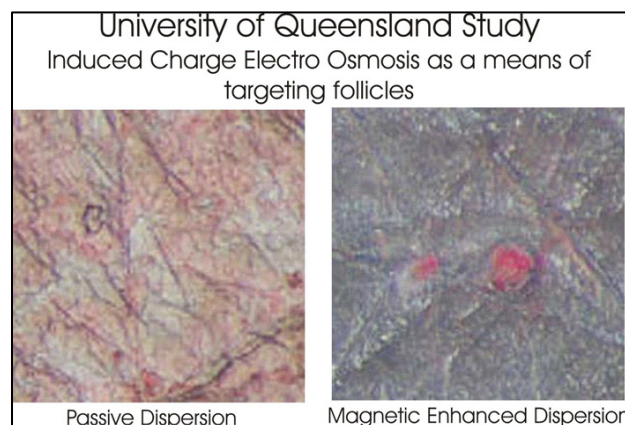
Magnetic fields will interact differently with regions of the skin with higher or lower conductivity (hydration), establishing regions of different electrical potentials. The movement of current (streaming potentials) created by the 3D field designed used by OBJ is believed to temporarily and reversibly alter the lipid packaging order, reducing local stratum corneum barrier function.

Water Binding

The relative balance of tightly and loosely associated water in the stratum corneum can influence the efficiency of the hydrophilic pathway. Induction by magnetic field in the case of Dermaportation, ETP and eM-patch has been shown to have direct influence on this relationship through the generation of induced streaming potentials

In the in vivo study (right) the potential for altered water distribution within the epidermis was investigated using AC skin Impedence and Capacitance, both established methods of monitors in vivo changes in dermal water distribution in real time.

The study investigated ETP with polyethylene occlusion against polyethylene occlusion alone. Statistically significant differences were observed indicating a magneto-hydration relationship.



6 PARTNERING

OBJ has development and testing facility that may be used in conjunction with various independent Universities and testing laboratories to provide a full suite of feasibility evaluations, POT and POC studies, formulation, product design, development, testing and manufacturing services.

Evaluation and Development Process

- **Proof of Concept**
Demonstrating efficacy or enhanced delivery with the target active
- **Optimisation**
Determining the best field structure for the preferred concentration and formulation
- **Pre-production**
Prototype development and efficacy and consumer testing
- **Production**
Manufacture and supply via a network of 3rd party contract manufacturers in Europe, USA and Asia

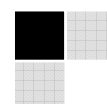
7 PUBLICATIONS AND PRESENTATIONS

Peer Reviewed Journal articles:

- *Enhanced Transdermal Delivery of Naltrexone by Pulsed Electromagnetic Fields in Human Skin In Vitro.*
Journal of Pharmaceutical Sciences 2009, [in press]
- Benson H. Krishnan G., Liew Y., Wallace V.P., Edwards J., *Enhanced skin permeation and hydration by magnetic field array: preliminary in vitro and in vivo assessment.*
Journal of Pharmacy and Pharmacology, 2009 Special Issue [in press]
- Namjoshi, S., Y. Chen, J. Edwards, and H.A.E. Benson, *Enhanced transdermal delivery of a dipeptide by Dermaportation.*
Biopolymers: Peptide Science, 2008.
- Namjoshi, S., R. Caccetta, J. Edwards, and H.A.E. Benson, *Liquid chromatography assay for 5-aminolevulinic acid: application to in vitro assessment of skin penetration via Dermaportation.*
Journal of Chromatography B 2007. 852[1-2]: p. 49-55.

Conference abstracts and Presentations:

- Namjoshi, S., H. Benson, Y. Chen, and J. Edwards. *Enhanced transdermal delivery of a dipeptide by Dermaportation.*
4th International Peptide Symposium. 2007. Cairns, Qld.
- Caccetta, R., M. Eijkenboom, J. Edwards, S. Namjoshi, and H. Benson. *Increased transdermal delivery of local anaesthetics by the novel penetration enhancement technology Dermaportation; in vitro and in vivo assessment.* in *PSWC*. 2007. Amsterdam.
- Benson, H., R. Caccetta, M. Eijkenboom, and J. Edwards. *Dermaportation treated skin is more permeable to Voltaren Emulgel.* in *World Congress on Inflammation*. 2007. Copenhagen.
- Krishnan, G., R. Caccetta, H. Benson, and J. Edwards. *Enhanced transdermal delivery of estradiol by Dermaportation.* in *Australasian Pharmaceutical Science Association Annual Conference*. 2006. Adelaide.



- Namjoshi, S., R. Caccetta, J. Edwards, and H. Benson. *HPLC assay for 5-aminolevulinic acid and its application to assessment of skin penetration*. in *Joint meeting of ASCEPT and APSA*. 2005. Melbourne.
- Benson, H.A.E., S. Namjoshi, and J. Edwards. *Dermal delivery enhancement by Dermaportation - a novel penetration enhancement technology*. in *39th Annual Conference of the Australian Society of Cosmetic Chemists*. 2005. Brisbane.
- Namjoshi, S., R. Caccetta, J. Edwards, and H.A.E. Benson. *Enhancement of skin penetration by Dermaportation*. in *Australasian Pharmaceutical Science Association Annual Conference*. 2004. Melbourne.

For more information please contact :

Jeffrey Edwards
Technical Director

OBJ Limited, 284 Oxford Street, Leederville, 6007 , Western Australia
M + 61 417912211 T +61 8 94433011 F + 61 8 94433866
E jedwards@obj.com.au Homepage www.obj.com.au

