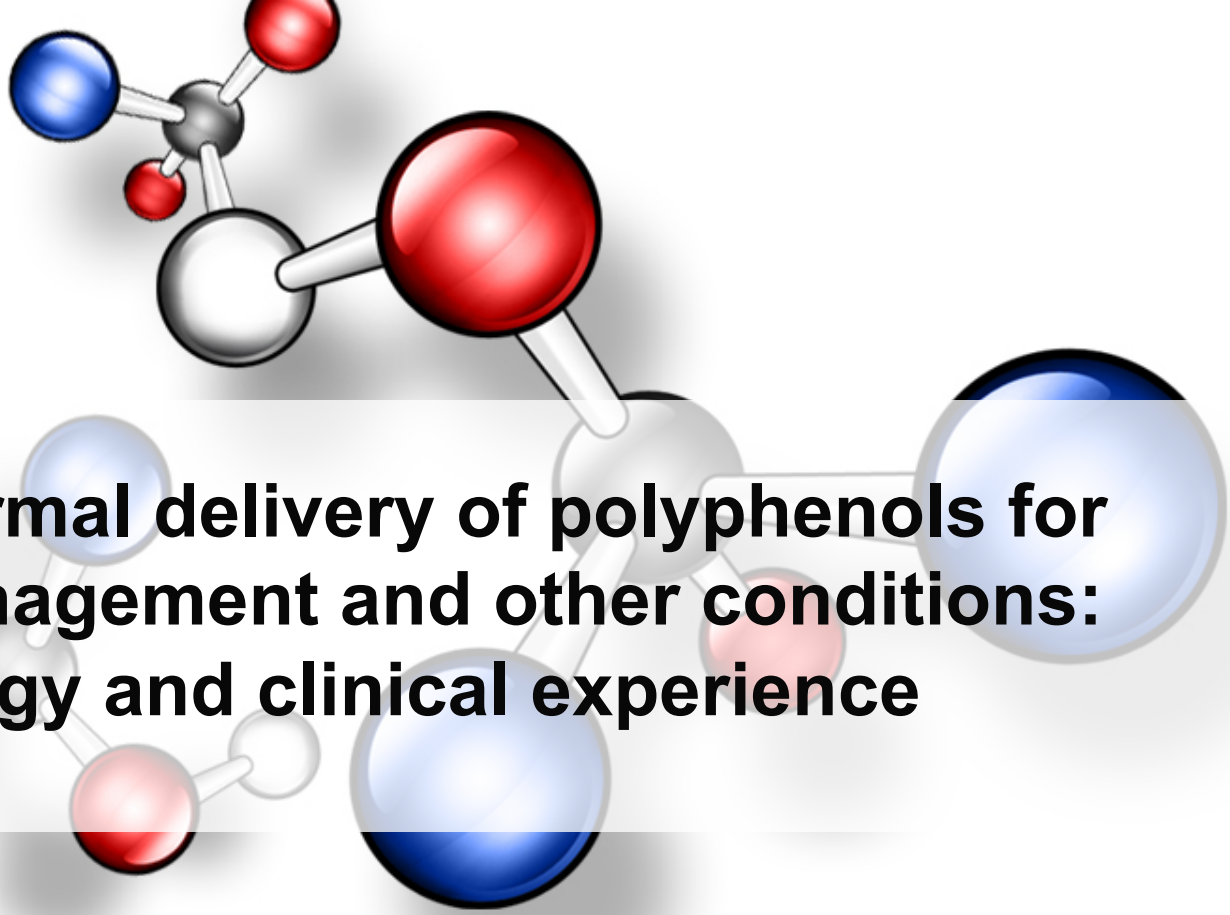


Transdermal delivery of polyphenols for pain management and other conditions: technology and clinical experience

Orthomolecular Conference
April 2014, Vancouver

Presented by Joseph Gabriele, PhD

Dr. Joseph Gabriele

- Molecular Pharmacologist.
- Research Scientist, National Research Council of Canada.
- University of Guelph Biomedical sciences and veterinary medicine.
- Ontario Mental Health foundation.
- Assistant professor – McMaster University, Canada.
- Postdoctoral Fellow, Queen's University, Department Of Psychiatry.

Key Learning Objectives

Key Learning:

- **New and Revolutionary Transdermal Pathway of Delivering Medications:**

  Overview of properties of revolutionary transdermal technological advances and evidence-based alternatives to oral and intravenous routes of medication delivery – a look at current innovations and future opportunities for natural and pharmaceutical product development.

- **Evidence-based Treatments:**

  A look inside the R&D process (pre-clinical R&D & human clinical trials) required to support the development, safety, and efficacy of new and superior, evidence-based natural products, combined with transdermal delivery routes. Products have been specifically formulated to target a variety of conditions in areas of critical healthcare need including: inflammation, joint pain, arthritis, circulation and venous insufficiency, muscle fatigue and fibromyalgia, and healing of wounds.

- **A superior way to treat patients:**

  An overview of general patient assessment principles that can be implemented in order to ensure the appropriate use of transdermal delivery and natural health product therapies in ways that can lead to successful patient outcomes.

Presentation Outline

1.
- Overview of transdermal drug delivery and current applications.
- Advantages of transdermal delivery.

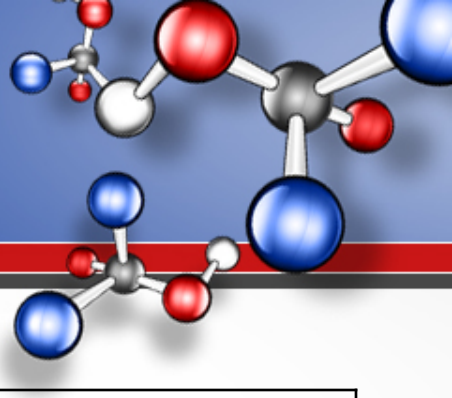
2.
- Rational design of a transdermal delivery systems and R&D for revolutionary new route to treat chronic and acute conditions, from pain to varicose veins to wound healing, etc.

3.
- Educating physicians and healthcare practitioners on therapeutic tools and use of new transdermal technologies to treat their patients efficiently and effectively, securing superior results (including case studies of positive treatment outcomes).

Overview of Transdermal Delivery

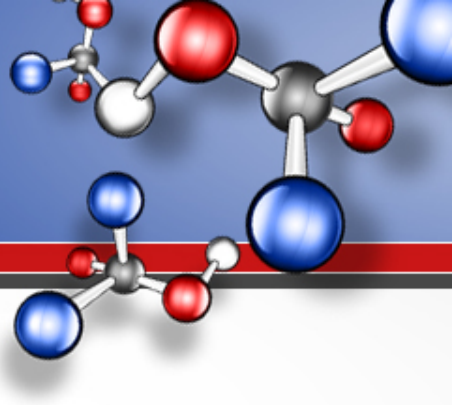
Need for Transdermal Delivery

Therapies That Use Transdermal Delivery of Drugs



Therapy	Drug Delivered
Motion Sickness	Scopolamine
Anti-angina	Nitroglycerine
Hypertension	Clonidine
Smoking Cessation	Nicotine
Hormone Replacement Therapy	Estradiol Estradiol/Progestin Testosterone
Pain Management	Fentanyl Lidocaine

Transdermal Drug Delivery



- Diffusion of drugs and natural molecules through skin into the dermis, muscle or systemic circulation for distribution and therapeutic effect.
- Most transdermal systems use passive delivery.
- Need to understand structure of human skin before designing delivery systems and determining potential applications.

Structure of Skin

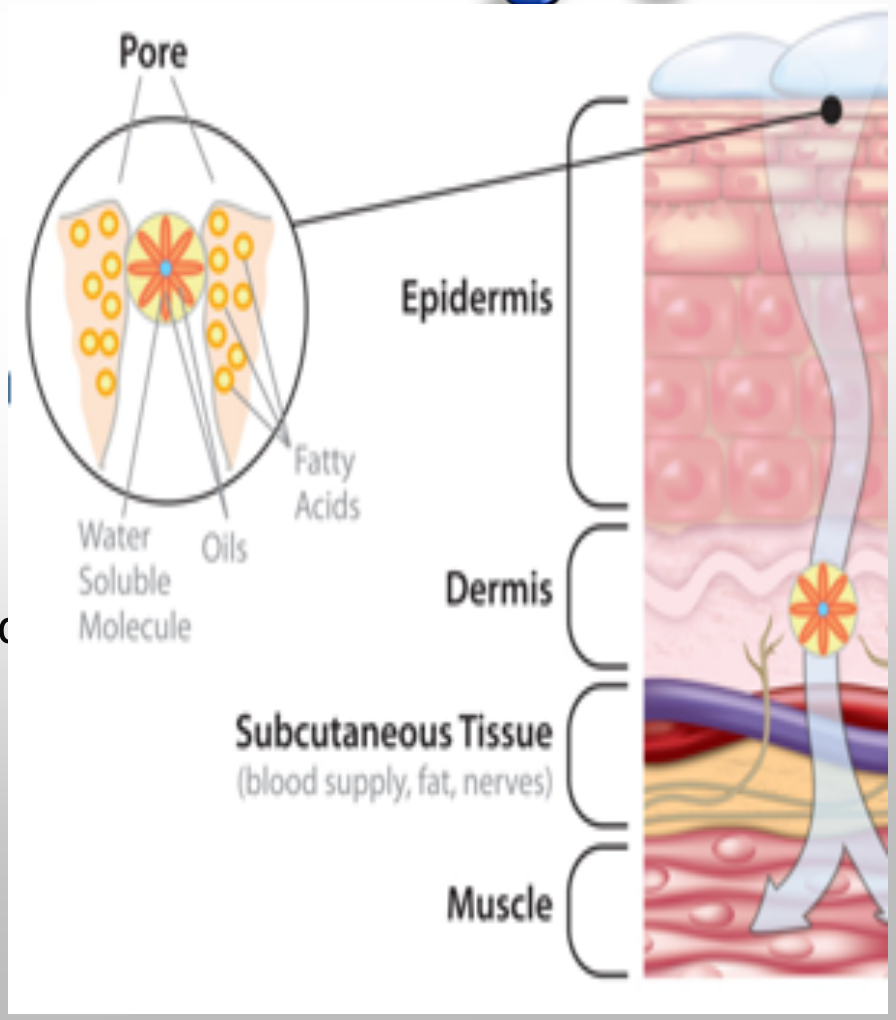
The human skin is composed of:

•*10-70 hair follicles and 200-250 sweat ducts/cm²* .

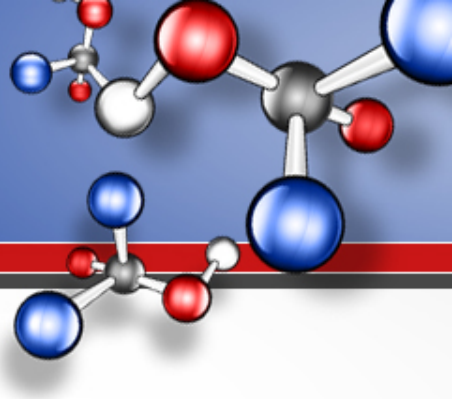
•It is one of the most readily accessible organs but difficult to penetrate.

•Approximately 2 m² surface area in adults and receives one-third of the blood circulating through the body.

•Skin as a port for drug administration recognized for several decades.



Structure of Skin

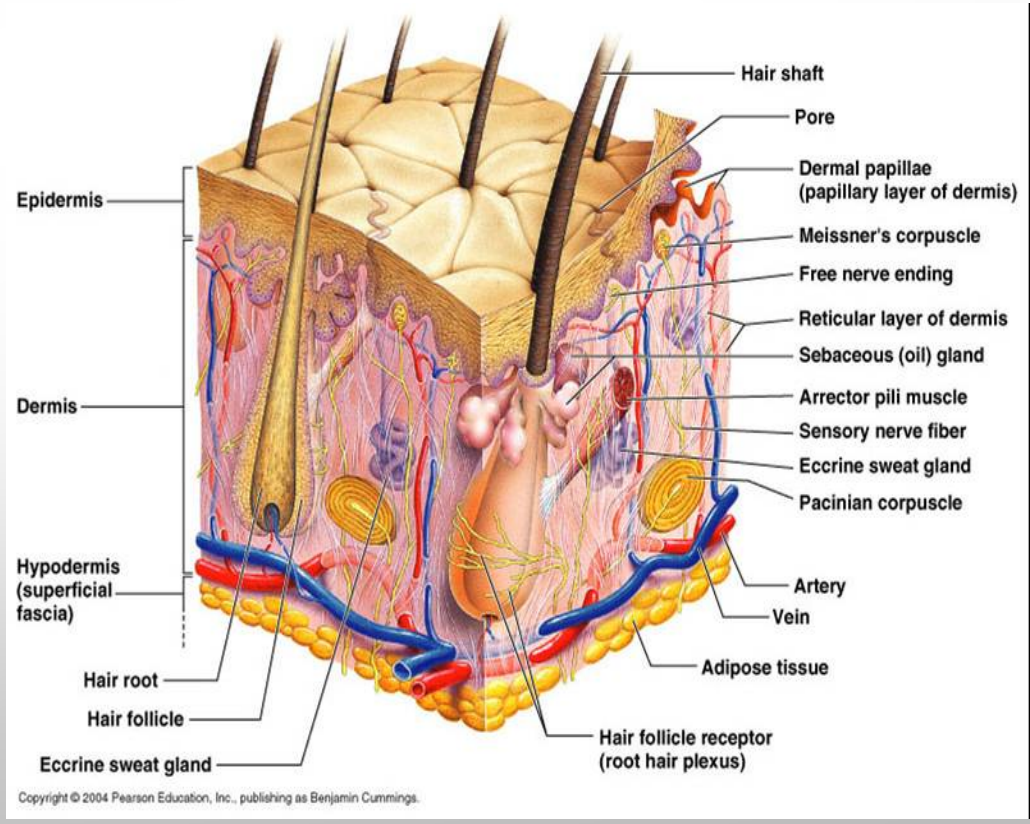


- 2 major layers of skin are the outer epidermis and the inner dermis.
- The epidermis:
  - stratified squamous keratinizing epithelial tissue.
  - Keratinocytes (abundant).
  - no capillaries present.
- The Dermis:
  - made of an irregular type of fibrous connective tissue.

Structure of Skin

- Subcutaneous tissue
  - mechanical cushion
  - thermal barrier
  - energy storage

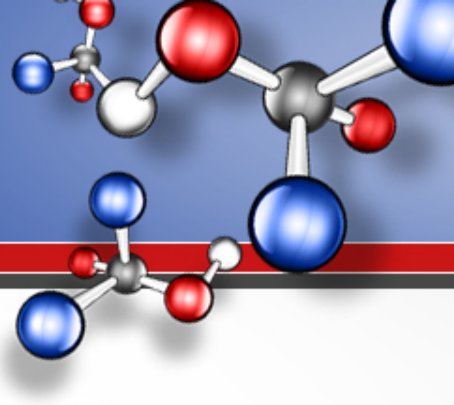
- Appendages
  - Sweat glands
  - hair follicles
  - Sebaceous glands
  - Nails



Skin Functions

- Physiological function
  - Produces vitamin D
- Protective function
  - Microbiological barrier
  - Chemical barrier
  - Radiation barrier
  - Temperature regulation
  - Immune response

Mechanisms of Transport

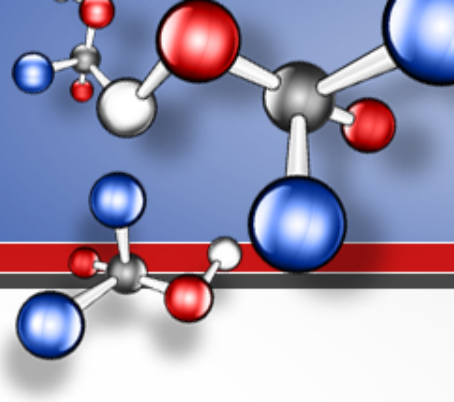


- Through skin pores, hair follicle, glands

- Through cells
  - Intercellular
  - Intracellular (transcellular)

- Drug transport depends on:
    - aqueous solubility and/or oil/water partition coefficient
    - concentration in the formulation vehicle,
    - the surface area of the skin to which it is exposed;
    - the thickness of the stratum corneum (inversely proportional)
    - The stratum corneum is thickest in the plantar (soles) and palmar regions and thinnest in the postauricular, axillary, and scalp regions of the body

Predictor of Transdermal Delivery



PERMEABILITY COEFFICIENT

Transport = Flux = (mg/cm^2/sec) = P x A x (C_d – C_r)

Permeability Coefficient = P = $\frac{D \times K}{h}$ (cm/sec)

Where

A = Surface area of application

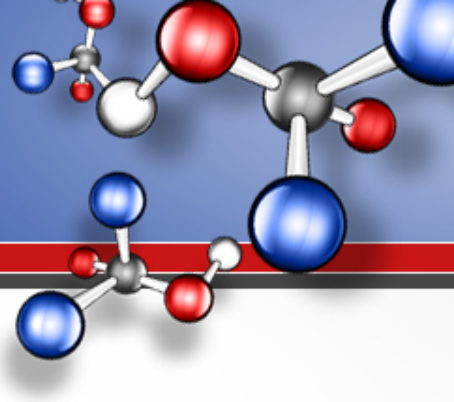
D = Diffusivity of drug in membrane (skin)

K = Partition coefficient (cream/skin)

C = Concentration in donor or receptor (cream or skin)

h = Thickness of membrane (skin)

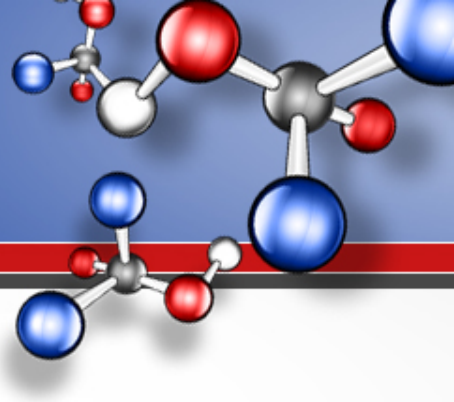
Transdermal Drug Delivery



Advantages:

- Steady permeation of drug across skin
- Controlled drug delivery
- Good for acid and enzyme reactive drugs
- Minimum risk of side effects
- Limited toxic effects
- Convenience: may require only once weekly.
- Easy drug administration
- Good for lipophilic drug molecules

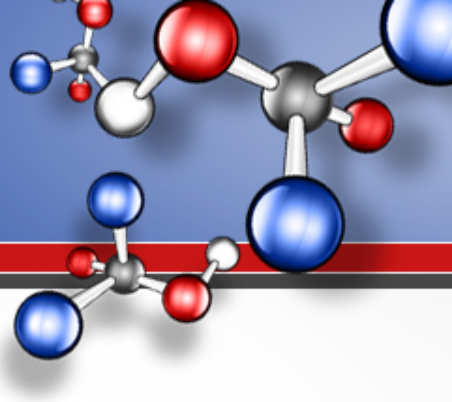
Transdermal Drug Delivery



Disadvantages:

- Possibility of a local irritation
- Allergic reactions are possible
- Risky for children
- Skin's low permeability
- Molecular size and polarity of drug
- Insufficient bioavailability
- If using patch, then damage to a transdermal patch

Attributes of a Passive Transdermal Drug Candidate



- Daily dose (< 20 mg/day)
- Half-life (10 hours or less)
- Molecular weight (< 500 daltons)
- Melting point (< 200 °C)
- Skin permeability
- Lipid solubility [partition coefficient (Log P) between –1.0 and 4]
- Toxicology profile

  (non-irritating and non-sensitizing to skin)

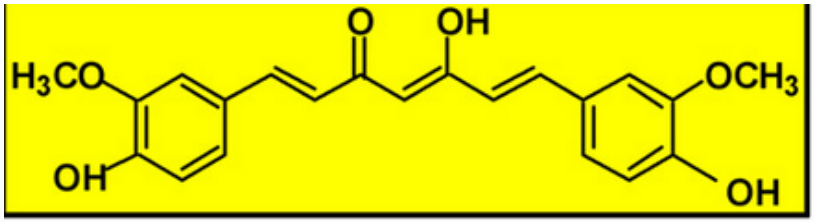
As technologies improve, the potential of drugs and attributes will expand

Transdermal Delivery R&D and Potential

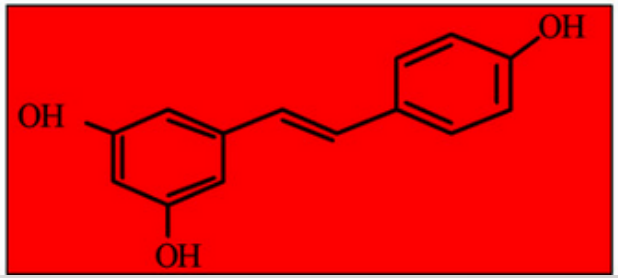
Trandermal Delivery of Natural Medicines

Transdermal technologies can now deliver the most stubborn molecules such as:

- Curcumin
- Ubiquinol
- Melatonin
- GABA
- Magnesium
- Berberine
- Amino acids
- Peptides



Curcumin



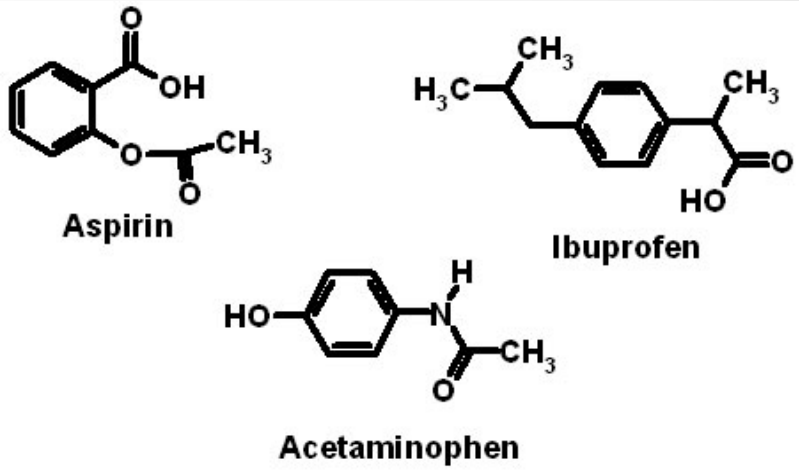
Resveratrol

The future of novel transdermal systems offers endless possibilities.

Pharmaceuticals Delivered Through the Skin

Transdermal delivery systems are currently being tested with different classes of pharmaceuticals to offer superior delivery, bioavailability, safety with less side-effects, and efficacy (both target specific and systemic):

- NSAIDs (melaxicam, ibuprofen)
- Statins
- Corticosteroids
- Anaesthetics (lidocaine, Xylocaine HCl)
- Bioidentical hormones
- Sildenafil

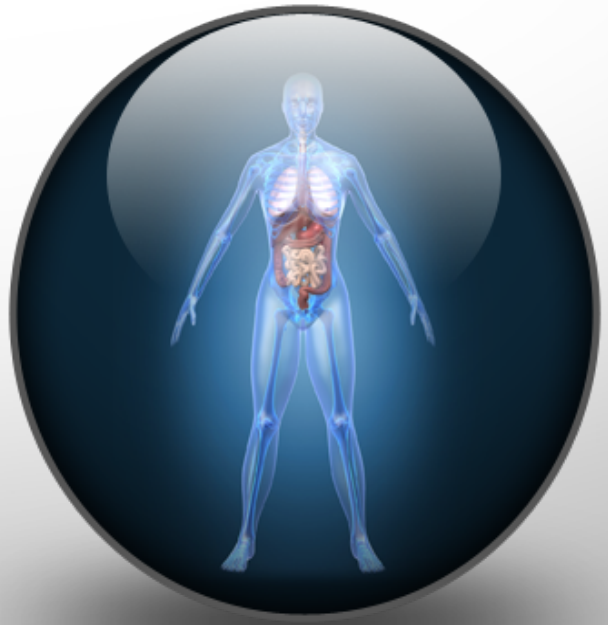


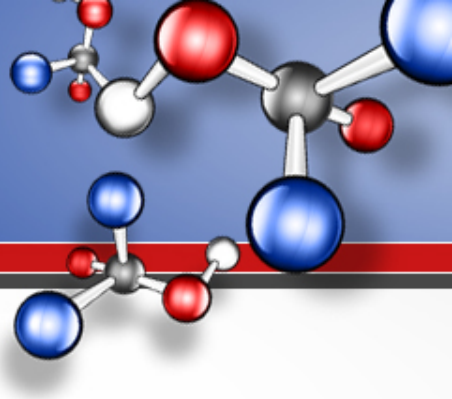
The future offers greater possibilities for drug delivery through the skin.

Advantages for Patient Care

Transdermal delivery is beneficial to patients and doctors

1. Avoidance of undesirable taste of oral medications, which can increase compliance.
2. Bypassing the gastrointestinal (GI) tract to prevent GI degradation and irritation.
3. Avoidance of partial first pass inactivation of active molecules in the liver.

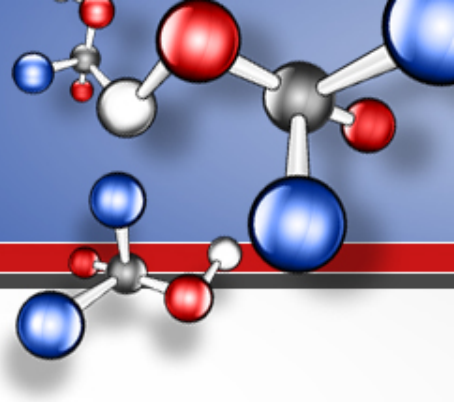




To achieve effective delivery through the skin and full potential, technologies must be improved…

Transdermal Drug Delivery

Strategies for improving transport rate



Penetration enhancers

(eg: Water, Terpenes, Oleic acids, Menthol, Azones)

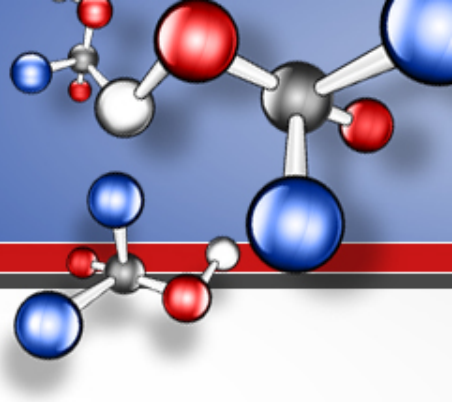
- Reduces barrier function of skin.
- Some penetration enhancers remove lipids from the skin
  - Water: a natural penetration enhancer.
  - Alcohol: a solvent as well as a penetration enhancer.

Natural and sustainable solutions in the transdermal pipeline

- Transdermal bases are now being created as natural pharma-based replacements for traditional synthetic, emollient-based creams currently used by hospitals, pharmaceutical and health sector manufacturers.
- Include all-natural oils and extracts and contain water soluble molecules.
- Broad-spectrum anti-microbial, anti-fungal, anti-bacterial and also contain anti-inflammatory properties.

Transdermal Drug Delivery

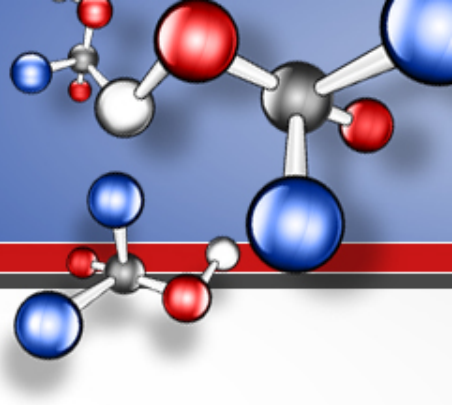
Strategies for improving transport rate



Liposomes (Lipid vesicles)

- Spherical vesicles with a membrane composed of a phosholipid bilayer.
- Created by sonicating phospholipids in water.
- Encapsulates drug molecule.
- Lipid bilayer can fuse with other bilayers.
- It neither penetrates nor fuses to SC.
- It can be sensitive to temp, pH, light etc.

Transdermal Drug Delivery
Challenges and Areas for Improvement

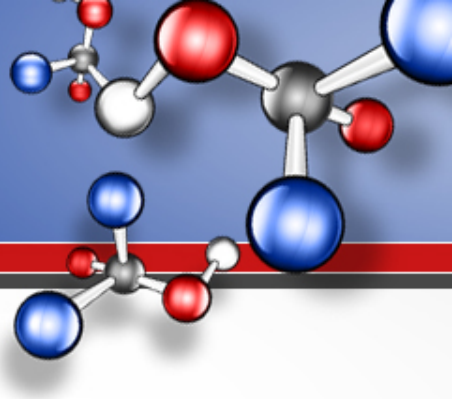


Absorption

- Transporting active molecules must be target-specific & sustainable by some kind of slow release mechanism.
- Ideal transdermal system shuttles both water soluble and fat soluble molecules across skin layers.
- Quick and effective penetration in significant concentration.

Challenges: Conjugation and strategic formulation of lead candidates and actives to control rates of absorption.

Transdermal Drug Delivery
Challenges and Areas for Improvement



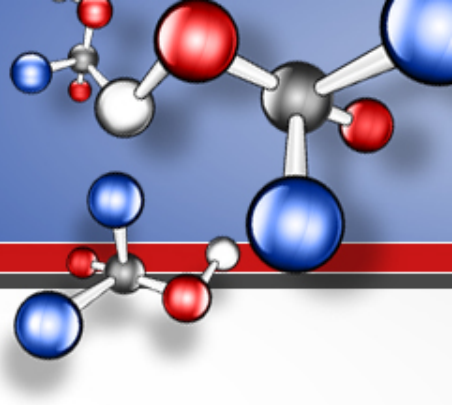
- **Polypharmacy** is the consumption of numerous natural molecules and/or pharmaceuticals taken at one time.

- Problem of medications counter-indicating and cross-reacting with each other, along with unwanted side- effects of overloading important organs like the liver and kidney.

- ***Developments:*** There are natural bases in the market now that can handle over 30% of a single molecule and/or polypharmacy using numerous water soluble and fatty molecules together.

- ***Challenges:*** Bringing multiple molecules (water- and fat-soluble) simultaneously to address a particular therapeutic need or disease-state and to determine the maximum window of natural molecules that can be compounded in these bases.

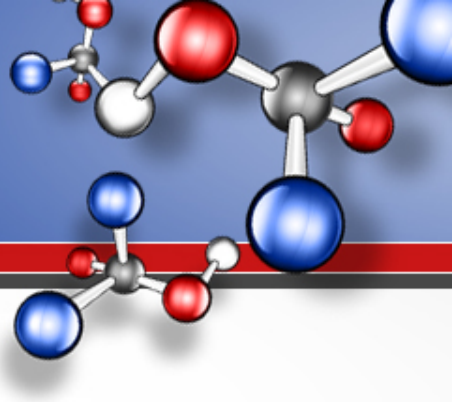
Transdermal Drug Delivery
Challenges and Areas for Improvement



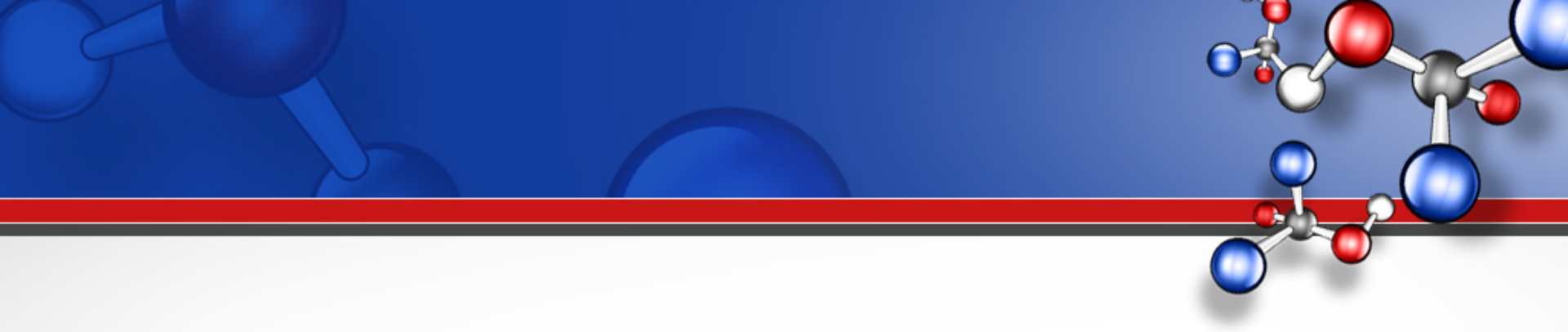
The "Molecule Size" Challenge

- Skin is the largest organ in the body (barrier to to environmental insults, pollutants, toxins, etc., and microbial organisms.
- Molecules < 500 daltons penetrate skin by simple diffusion and/or with enhancer carrier molecules.
- ***Developments:*** Current transdermal bases have brought across the skin water-soluble molecules as large 857 Daltons through strategic conjugation. Molecules are also encapsulated by use of fatty acids to form liposomal structures around the water soluble molecules for better skin penetration.
- ***Challenges:*** Challenges in the field are to transport numerous larger molecules (> 500 Daltons) across the skin, and in active form (e.g. enzymes, larger proteins, etc.).

Transdermal System Design: What's Ahead?



- Delivery of larger molecules using enhanced passive and active delivery systems
- Materials and formulations to reduce skin irritation, enhance the adhesion profile, and improve comfort and wear
- Transdermal technologies (e.g. patches) with specialized drug delivery profiles
- Treatments with features that aid in application and use
- User and environmentally-friendly packaging designs (e.g. monodose packaging).



Case Studies and Take-Home lessons of Transdermal Delivery

Case Study 1 – Transdermal Delivery and Targeted Pain Treatment

Pain Statistics

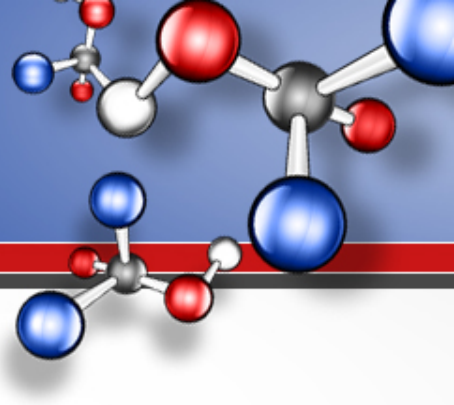
- Pain is a major concern for older adults because of its high prevalence – estimated to be as high as 65% for those living in the community and up to 80% of older adults living in long-term care facilities.

- Chronic pain costs more than cancer, heart disease and HIV combined with direct health care costs of $6 billion.

- Productivity costs related to job loss and sick days are estimated to be $37 billion per year.

Need for more sustainable pain treatments – transdermal delivery offers a hope

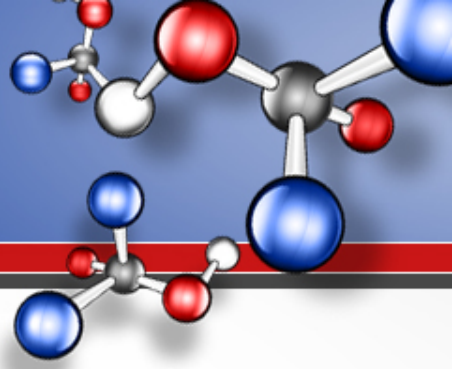
Case Study 1 – Bursitis and Inflammation



Case study (Joan L.)

- 52 years old, suffering from bursitis in shoulder for over 20 years with nighttime headaches and trouble sleeping.
  - Treatment regimens of over-counter-drugs failed.
  - Acupunncture worked but became too expensive.
  - Tried transdermal cream containing an active rutin that has significantly relieved pain.

Why Transdermal Therapy Worked?

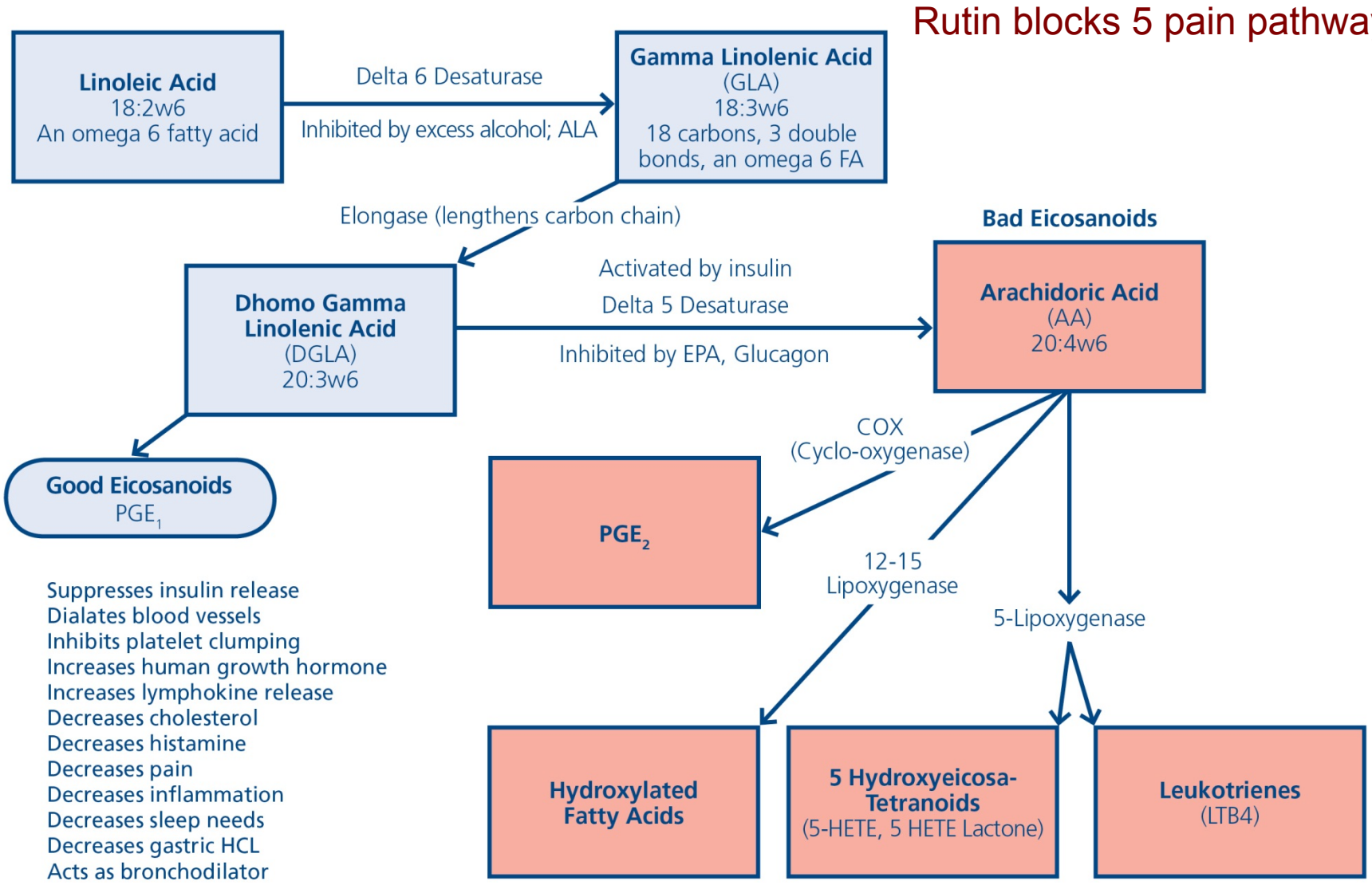


Advanced transdermal delivery systems can now penetrate therapeutic water-soluble molecules 6x deeper than ever before.

Choice of active molecules is important:

- Rutin is a potent anti-inflammatory and analgesic.
- 610 Dalton water-soluble flavonoid found in barley, wheat, and orange peel.
- When combined with other flavonoids, catechins, and carotenoids and a **sustainable delivery system**, rutin brings about significant and targetted relief of pain and inflammation (including bursitis).

The Inflammatory Pathways



Why Transdermal Therapy Worked?

Rutin blocks 5 pain pathways when delivered deep into the skin:

- **Inhibits Nitric Oxide Pathway -** this pathway causes inflammation via inducible nitric oxide synthase.

- **Inhibits Histamine Pathway -** this pathway another mediator of inflammation- Rutin known to act on histamine on the gene level.

- **Inhibits Arachidonic pathway -** This pathway through cyclooxygenase mediates inflammation through prostaglandins and leukotrienes.

- **Inhibits Protein Kinase C Pathway -** this pathway involved in formation of thromboxane A2, involved in platelet aggregation.

- **Inhibits cGMP/ Protein Kinase G pathway -** This pathway involved in mediating inflammation and is the switch between acute and chronic pain.

Case Study 2 – Transdermal Delivery and Targeted Varicose Vein Treatment

Varicose Veins

What are Varicose Veins?

- Chronic venous insufficiency occurs when the leg veins do not allow blood to travel back to the heart. (Arteries carry blood away from the heart, while veins carry blood to the heart).

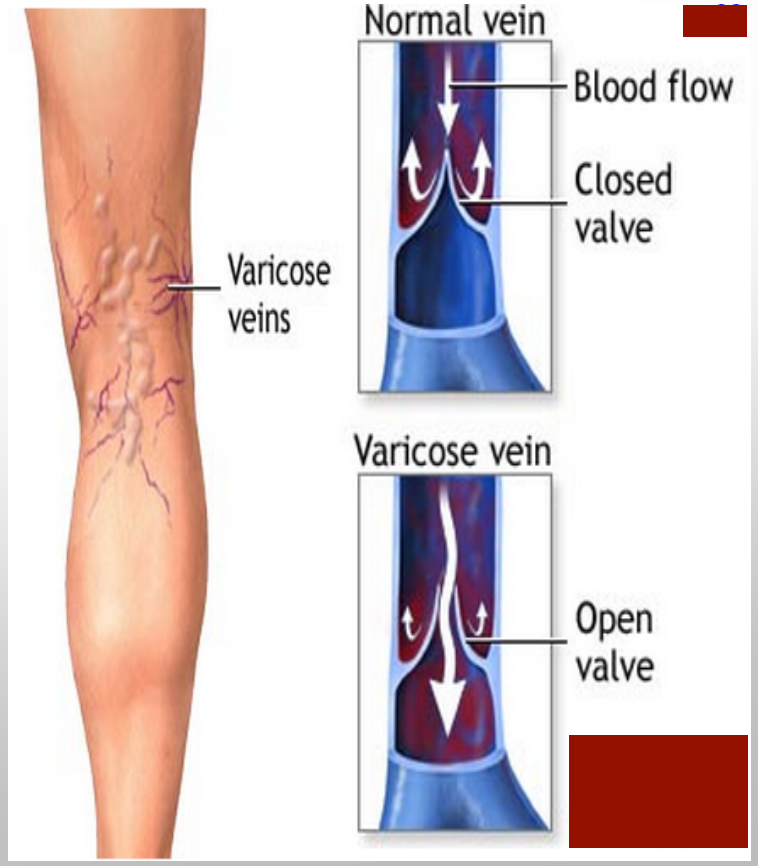
- The condition affects about 5% of the US population.

- Causes: Obesity, genetics, high blood pressure, lack of exercise, smoking, phlebitis (swelling and inflammation of a superficial vein, blood clot and more.

Varicose Veins

What are Varicose Veins? (continued)

- Varicose veins are gnarled, enlarged veins close to the skin's surface.
- To prevent back flow, tiny valves in the veins close at regular intervals. If these valves leak, the blood cannot move forward and a reversed flow occurs called reflux.
- *Therapies:* surgery, compression garment.



Case Study 2 – Varicose Veins

Case study (ML)

- 76 year old female, suffering from varicose veins and resulting pain.
  - Tried compression garments but pain was severe.
  - Physical appearance of veins persisted.
  - Was not comfortable with surgery, which was expensive and no longer covered by the healthcare system.
  - Tried a topical varicose vein cream delivered deep through the skin and experienced significant improvement in appearance and reduction of pain in ~6 weeks of consistent use.

Why Transdermal Therapy Worked?

Effective penetration of efficacious ingredients such as:

Witch hazel

- Latin name: *Hamamelis virginiana* L.
- The tannins, volatile oils, gallic acid, resin, flavonoids (procyanidins), and other natural components in it give witch hazel its astringent, antibacterial, antiviral, anti-inflammatory (pain-relieving) and antiseptic qualities.

Why Transdermal Therapy Worked?

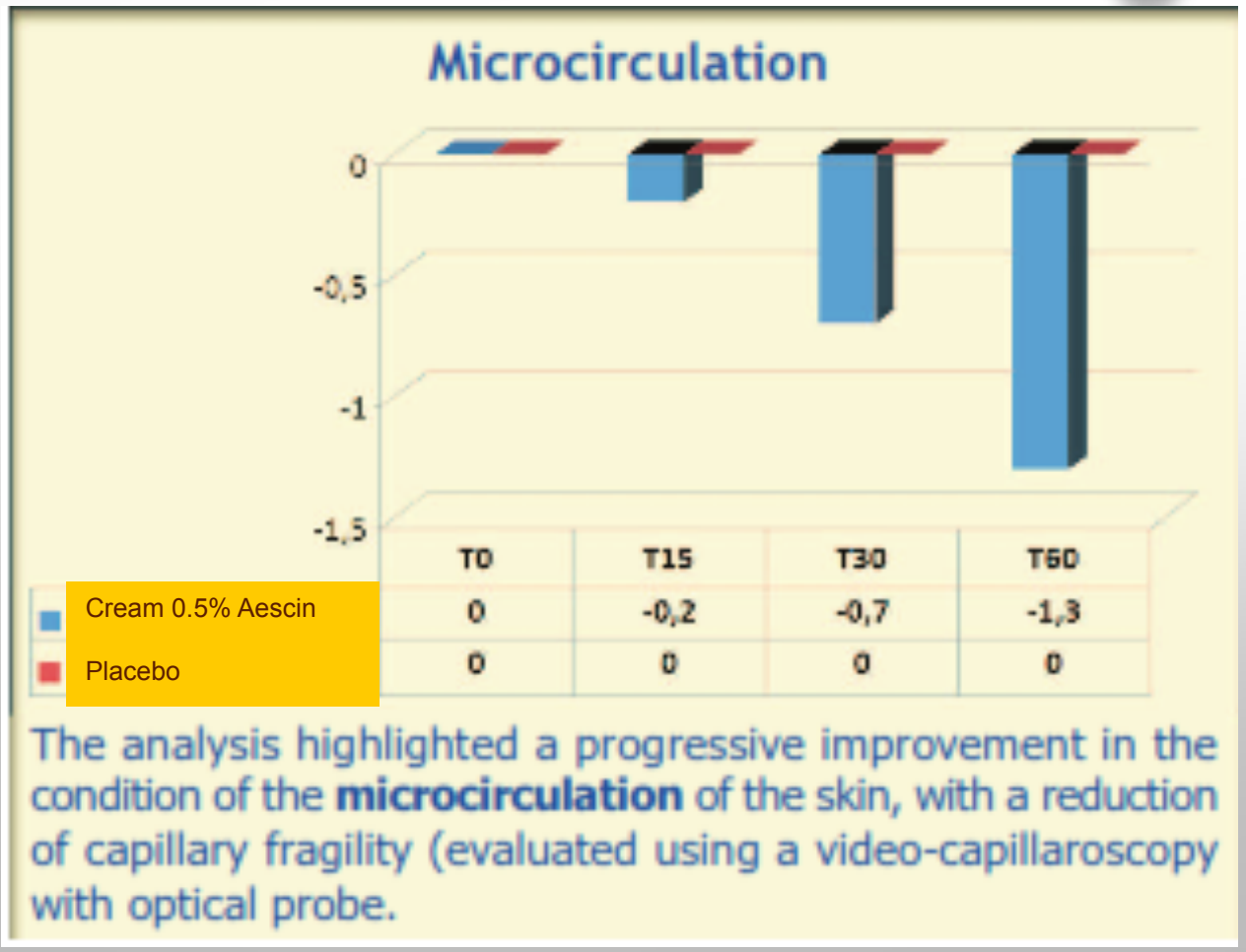
Effective penetration of efficacious ingredients such as:

Horse chestnut

- An anti-inflammatory, astringent, antispasmodic, and reduces swelling.
- AESCIN, horse chestnut's main active constituent, reduces capillary permeability and improves venous tone, which results in smaller veins and decreased pain.
- Aescin has been shown to prevent key enzymes from breaking the walls of capillaries.

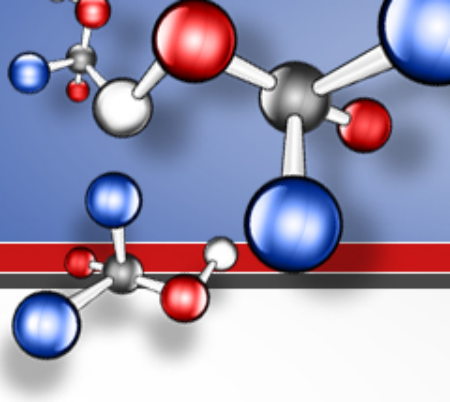
Adapted from Google Images

Aescin delivered transdermally



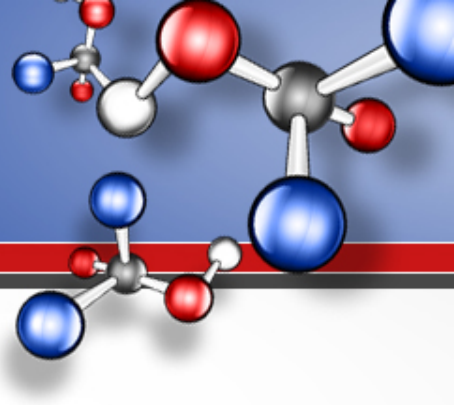
The analysis highlighted a progressive improvement in the condition of the **microcirculation** of the skin, with a reduction of capillary fragility (evaluated using a video-capillaroscopy with optical probe.

Transdermal Delivery System Benefits Summary



1. Technologies can now clinically deliver medications deeper than ever before possible with ongoing improvements in molecule size, absorption, and polypharmacy.
2. Ability to effect relief with natural molecules (and pharmaceuticals); systems are aligned with health healthcare professionals ie. Naturopaths, Chiropractors, Physiotherapists and massage therapists.
3. Proven Sustainability: Systems can now deliver ingredients which are time released requiring less frequent application; deeper penetration = lower doses.
4. More actives (polypharmacy) can be delivered in a functional form.
5. Transdermal delivery is a safe, targeted when needed, and more effective alternative to oral pain medication.

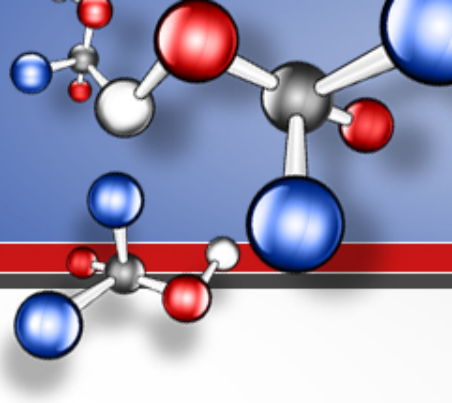
Transdermal Delivery Systems Conclusions



1. Transdermal delivery technologies are becoming one of the fastest growing sectors in the pharmaceutical industry.

2. Advances have brought about benefits for both patients with fewer side-effects than other routes such as oral delivery and increased efficacy; physicians in turn benefit from increased patient compliance.

3. The market value for transdermals in US in 2005 was $12.7B and is expected to increase to $31.5B in 2015 – with significant growth potential in the next 10 years.



Thank You for your participation.

Questions?