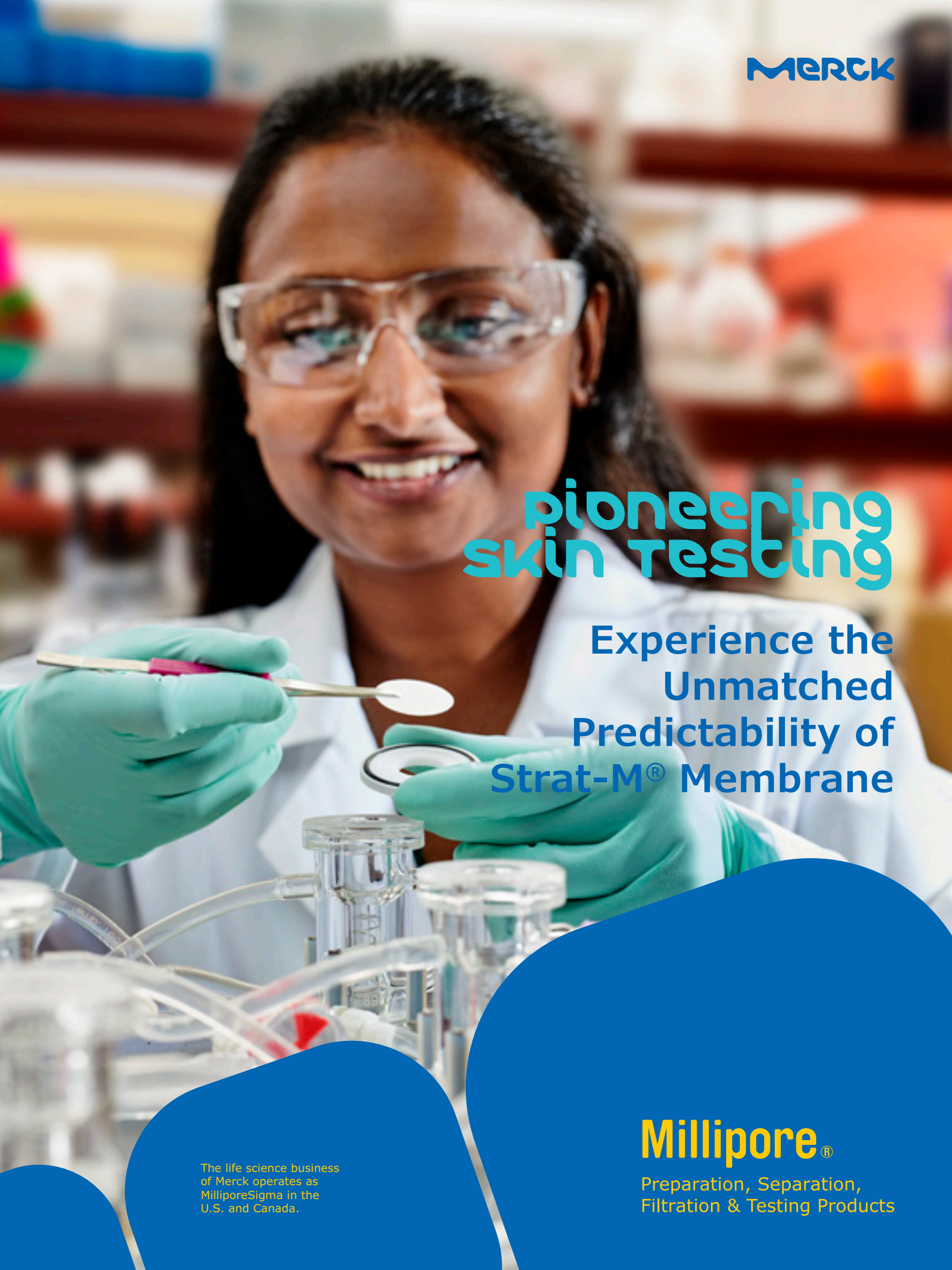

MERCK

Pioneering Skin Testing

Experience the Unmatched Predictability of Strat-M® Membrane

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Millipore®

Preparation, Separation, Filtration & Testing Products

A Skin Model for Formulation Screening and Optimization

Topical or transdermal delivery of pharmaceuticals or personal care actives provides an alternate painless route of delivery for compounds especially when local delivery of active is preferred over systemic delivery. Additional benefits of this delivery method include ease of application and patient compliance as compared with oral or parenteral delivery.

In-vitro permeation testing (IVPT) is one of the most commonly used tests during formulation development and optimization for transdermal and topical formulations. This test helps distinguish between different formulations of the same active and allows for progressing the appropriate formulation into pre-clinical and clinical phases. Human skin (from cadavers or cosmetic surgery) is considered a gold standard for diffusion profiles in these studies. Animal skin (pig, rat, mouse etc.) can also be used as a surrogate for human skin in these studies, but both human and animal skin suffer from biological variability that can make correlations difficult.

Strat-M® membrane, a synthetic non-animal based model* useful for predicting human skin diffusion, correlates more closely to human skin than animal skin models commonly used for IVPT of transdermal formulations. Since it is a synthetic test model with low variability and no special storage or hydration requirements, Strat-M® membrane simplifies experimental design and data analysis.

*For research use only. Not for use in diagnostic procedures.

Looking at the pharmaceutical & personal care work flow, Strat-M® membrane can be used where biological models are traditionally used.

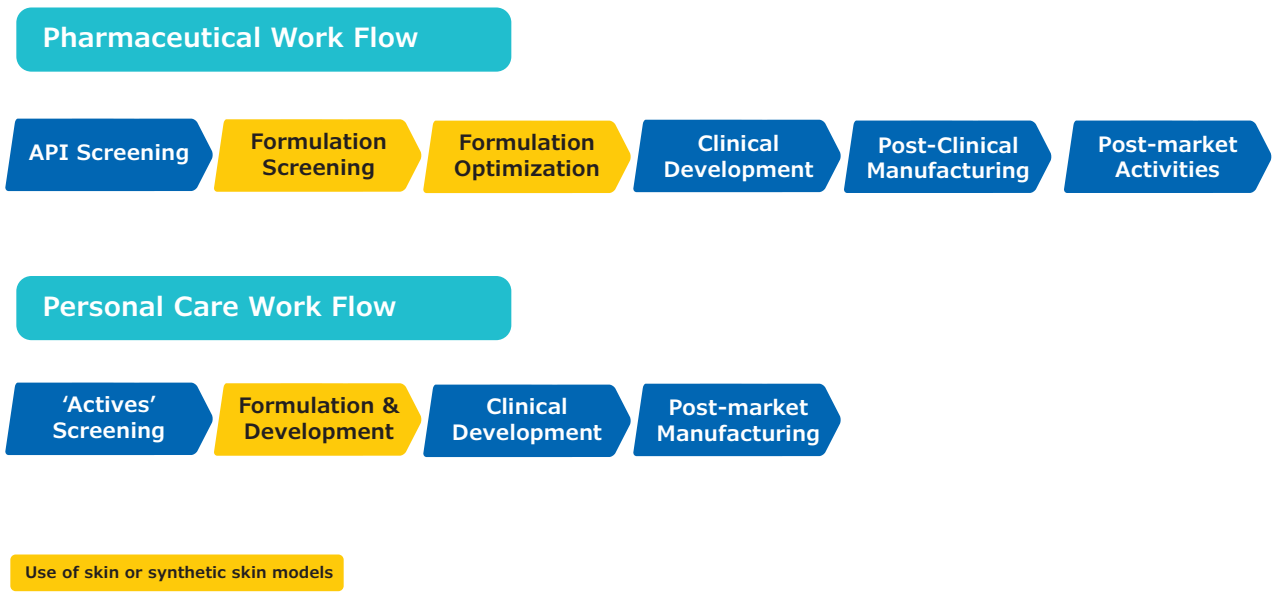

Figure 1: Pharmaceutical and Personal Care work flow and Use of Skin Models for *in-vitro* testing

Some common studies carried out during formulation optimization are as follows:

1. Formulation rank ordering with formulations containing different % of API.
2. Testing extended release patches.
3. Evaluating encapsulated and un-encapsulated sunscreen active components.

A perfect fit for Franz cells

Franz diffusion cells are commonly used in this arena for developing and optimizing formulations. A Franz cell consists of a donor and acceptor chamber which is separated by a diffusion membrane (human skin or Strat-M® membrane). The donor chamber contains the formulation under study whereas the acceptor chamber contains aqueous buffer maintained at 32 or 37 ºC with constant stirring. An intimate contact of membrane to both phases allows for diffusion of active from donor chamber to acceptor chamber. In the case of most commercially available Franz diffusion systems, it's very easy to change from an animal skin model to Strat-M® membrane. When using Hanson diffusion testers, a special donor cell is required for leak free operation of the diffusion tester.

Figure 2: An example of Vertical Franz Cell set up commonly used in IVPT studies. Strat-M® membrane is compatible with a wide range of Franz diffusion cell set ups.

Strat-M® Membrane – a synthetic transdermal diffusion test model

Engineered for performance

We've engineered predictive performance into the structure and chemistry of the Strat-M® membrane. Like human skin, the Strat-M® membrane has multiple layers with varied diffusivity, as shown in Figure 3.

Strat-M® is constructed of two layers of polyethersulfone (PES, more resistant to diffusion) on top of one layer of polyolefin (more open and diffusive). These polymeric layers create a porous structure with a gradient across the membrane in terms of pore size and diffusivity. The porous structure is impregnated with a proprietary blend of synthetic lipids, imparting additional skin-like properties to the synthetic membrane.

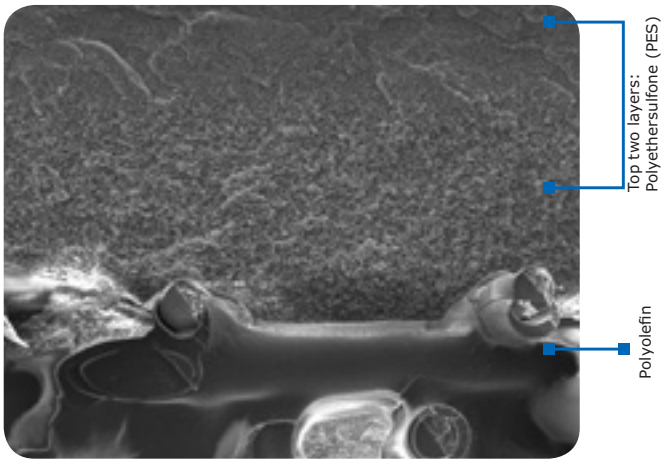

Figure 3: Scanning Electron Micrograph (SEM) of Strat-M® membrane shows very similar multi layer structure between human skin and Strat-M® membrane.

Strong correlation to human skin

We observed nearly equivalent flux of 21 test compounds ranging in molecular weight from 122 to 491 with log P values (representing relative lipophilicity) of -2.53 to 6.78 through human skin (split thickness cadaver skin) and Strat-M® membrane. These data indicate that Strat-M® membrane has broad chemical compatibility and is an appropriate model for screening compounds with diverse physiochemical properties.

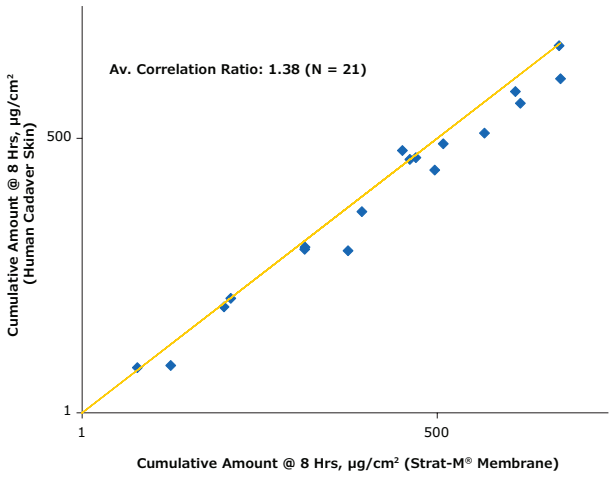

Figure 4: Strong correlation for diffusion of 21 different compounds with varying physico-chemical properties. Yellow line represents one to one correlation between human skin and Strat-M® membrane whereas the blue dots represent actual cumulative diffusion (µg/cm²) of compounds at 8 hrs. All the data points are very close to the ideal correlation with an average correlation ratio of 1.38

Strat-M® membrane correlates better to human skin compared with other biological models

Many researchers are using animal skin as a surrogate for human skin in IVPT studies because human skin is either difficult to obtain or in many countries it cannot be used for *in vitro* research. Pig, rat or mouse skin are commonly used as surrogates for human skin. Sometimes even human skin tissue grown in a multi well plate is used as a surrogate in place of human skin. The data below show that Strat-M® membrane correlates betters to human skin compared with some of these animal skin models. For acetylsalicylic acid (aspirin, an analgesic), high flux was measured through both human skin and Strat-M® membrane; however, flux was lower through porcine skin, indicating that Strat-M® membrane is a better match for human skin than animal skin models.

The second data set shows comparison of dexamethasone diffusion; both human skin and Strat-M® membrane have similar low flux whereas rat skin and engineered skin show very high flux.

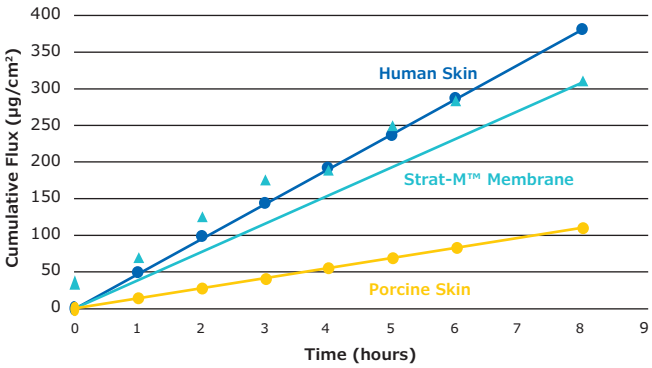

Figure 5A: Acetylsalicylic acid diffusion. The diffusion rate of acetylsalicylic acid through Strat-M® membrane was measured on a Franz diffusion cell apparatus (0.635 cm²). Six Franz cells were used. The donor compartment of each cell was loaded with 500 µL of a saturated acetylsalicylic acid solution. Diffusion performance was compared to published values for 8-hour cumulative diffusion through human cadaver and porcine skin. Data represent average cumulative flux at each test point.

Sources - Human Cadaver Skin: International Journal of Pharmaceutics, 2006, vol 310, pg 31-36; Porcine Skin: International Journal of Pharmaceutics, 1999, vol 181, pg 255-263.

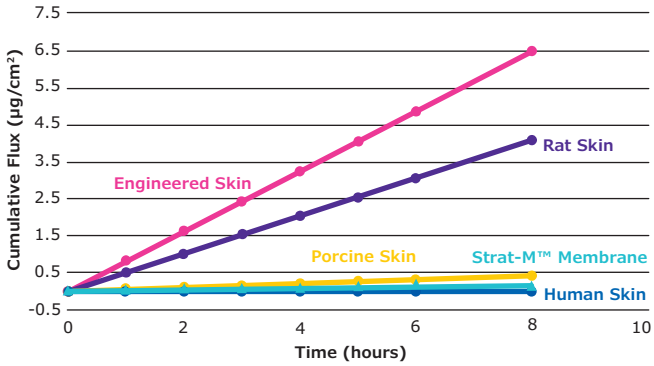

Figure 5B: Diffusion of dexamethasone through human skin and Strat-M® membrane compared against diffusion through pig skin, rat skin and engineered skin.

Sources - Human Cadaver, Rat, Engineered Skin: Archives of Practical Pharmacy, 1998, vol. 58, pg 155-163; Porcine Skin: Physical Therapy, 2008, vol. 88, pg 1177-1185.

Formulation development

Delivering an appropriate amount of active into skin or through skin into systemic circulation is a key goal of formulation development. Modulating either the amount of active diffusing into skin/circulation or modulating the rate of active delivery is key to success in formulation development. Some of the most common experiments conducted as part of formulation optimization are as follows,

1. Creating various formulations containing different amounts of active – These studies help understand the amount of API diffusing into systemic circulation and help rank order formulations allowing maximum amount of API diffusion into systemic circulation over a period of time.
2. Creating formulations containing different forms of active ingredient – These are formulations containing the same % of active within the formulation, but the active component itself is in different forms (encapsulation of active, different isoform, different salt form, etc).
3. Extended release formulation development – Formulations which allow for delivery of active over an extended period of time are always considered user friendly since they reduce frequency of dosing for a patient and lead to better patient compliance.

Formulation rank ordering:

When tested against 3 different Lidocaine formulations containing 2, 4, and 5% Lidocaine, Strat-M® membrane and human skin provide the same rank ordering when it comes to diffusion of API into receptor medium. The high variability seen with human skin makes it difficult to compare these data sets to provide a clear idea on rank ordering between different formulations, whereas Strat-M® membrane with its low variability provides data that is distinct from each other allowing for comparison of data sets between different formulations.

Table 1: Rank ordering of Lidocaine formulations containing different amounts of Lidocaine using Strat-M® membrane and Human cadaver skin

Rank Order	Human Skin	Strat-M® Membrane
1	2% Lidocaine Gel	2% Lidocaine Gel
2	4% Lidocaine Gel	4% Lidocaine Gel
3	5% Lidocaine Patch	5% Lidocaine Patch

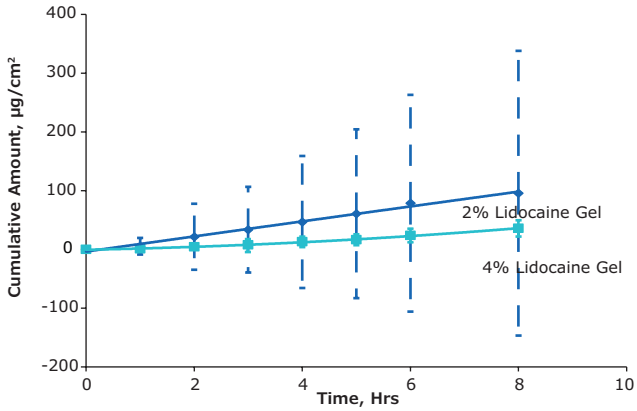

Figure 6A: Diffusion of Lidocaine through human cadaver skin, high variability makes it difficult to distinguish between two data sets.

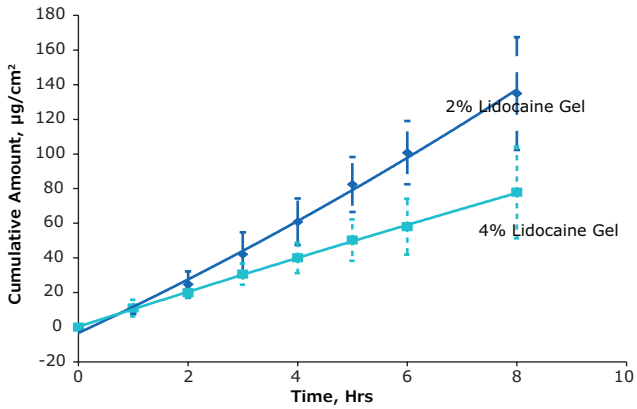

Figure 6B: Diffusion of Lidocaine through Strat-M® membrane, low variability of Strat-M® membrane clearly allows distinguishing between the two data sets to help move the right formulation forward in drug development.

Use of Strat-M® membrane to distinguish between different forms of active

One area of formulation development is testing alternative forms of an active. For sunscreen actives to prevent sun damage, they need to stay on the skin surface and not diffuse through into active circulation. Sunscreen actives can lead to undesired side effects when they diffuse through skin into active circulation. Octocrylene is one such sunscreen active which is known to be a photo sensitizer when absorbed into skin leading to formation of free radicals within skin.

In this example we show two different forms of octocrylene in an emulsion formulation. The data shows that encapsulated octocrylene does not diffuse through Strat-M® membrane similar to human skin.

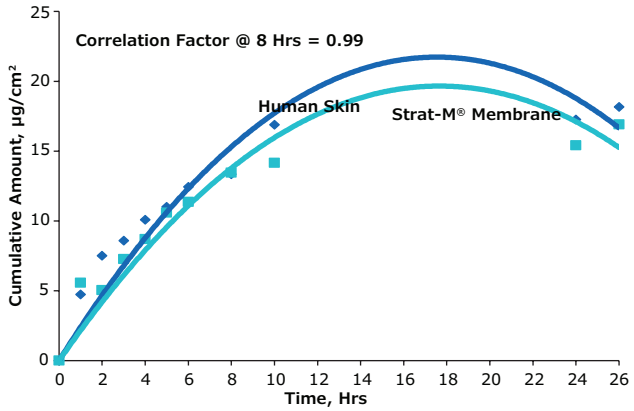

Figure 7A: Diffusion of Octocrylene through human skin and Strat-M® membrane shows close correlation between them.

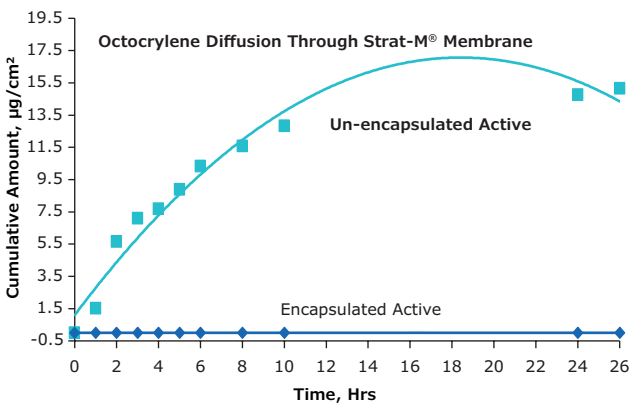

Figure 7B: Octocrylene diffusion is reduced significantly when it is encapsulated as seen in the chart above.

Stability of Strat-M® membrane lends itself to long term diffusion studies - development of extended release formulations

Extended release formulations allow actives to be delivered through skin over an extended period, providing consistent levels of active where it is needed. These formulations also significantly reduce dosing frequency which can be beneficial for patient compliance for chronic conditions.

One such example is the ethinyl estradiol patch which is a weekly patch used for pregnancy prevention. Since human skin deteriorates in 20/24 hrs under IVPT experimental conditions it is very hard to do extended release IVPT studies using human or animal skin models. Strat-M® membrane can be easily used for long term diffusion studies because it is stable under these experimental conditions.

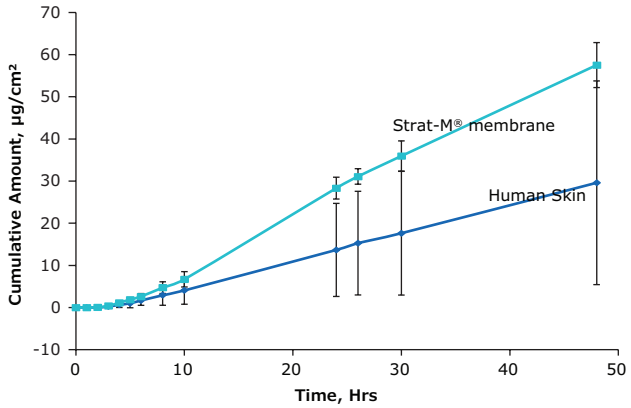

Figure 8: Diffusion of Ethinyl estradiol through human skin and Strat-M® membrane shows that because of high stability of Strat-M® membrane it allows it to be used for long term diffusion studies, whereas human skin degrades after 24 hrs of diffusion studies.

High variability associated with this skin study for 48 hours indicates deterioration of skin beyond ~20 hours. On the other hand, Strat-M® membrane shows consistently low variability even at 48 hours indicating the utility of Strat-M® membrane for long term IVPT studies.

Use of Strat-M® membrane for *in-vitro* release testing (IVRT)

IVRT is an essential quality control test required prior to releasing a manufactured lot to market. It is used to verify lot to lot consistency of topical/transdermal formulations. These tests are conducted in the same fashion as IVPT studies using a Franz diffusion cell set up. A membrane is required to separate the formulation from receptor fluid used in these studies. Commonly, hydrophilic PTFE, PVDF or PES membranes are used as a porous barrier in these studies. Strat-M® membrane can also be used for these studies as it provides a porous barrier between formulation and receptor media.

Ultimate Experimental Convenience with Strat-M® Membrane

- Very low variability alternative (CV = 8%) to human and animal skin
- Strong correlation (Correlation Factor = 1.38) to human skin and is suitable for screening new actives as well as formulation optimization
- Long shelf life, experimental convenience, ease of availability and minimal safety hazards

Read the peer-reviewed articles citing Strat-M® membrane: **SigmaAldrich.com/strat-m**

Ordering Information

Description	Cat. No.
Strat-M® Membrane, 25 mm, 60/pk	**SKBM02560**
Strat-M® Membrane, 47 mm, 60/pk	**SKBM04760**

To learn more and order the Strat-M® membrane, please visit:
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