



Effect of Penetration Enhancers on the Percutaneous Delivery of Pain Management Actives



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INTRODUCTION

Analgesic therapies for acute and chronic pain conditions currently rely on three major classes of drugs: 1) nonsteroidal anti-inflammatory drugs, 2) opioids, and 3) a group of drugs with diverse pharmacological actions collectively known as adjuvants.¹ By definition, topical drugs used to control pain will act locally on damaged or dysfunctional soft tissues or peripheral nerves. Nonsteroidal anti-inflammatory drugs are among the most widely used of all therapeutic classes of drugs. Opioid drugs act on receptors present on the peripheral terminals of thinly myelinated and unmyelinated cutaneous sensory fibers. Adjuvant drugs acting on voltage-gated channels play a fundamental role in the control of neuronal excitability. Adjuvant drugs acting on gamma-aminobutyric acid receptors can modulate peripheral pain signaling. Adjuvant drugs acting on acute musculoskeletal pain are a misnomer because most medications in this class have little or no direct action on the contractile mechanisms of striated skeletal muscle. Adjuvant drugs acting

on *N*-methyl-D-aspartate receptors are proposed for the treatment of neuropathic pain. Adjuvant drugs acting as an antidepressant can treat pain by adjusting levels of neurotransmitters.

In this work, novel pain management formulations are presented for skin delivery. With the aim of incorporating baclofen, bupivacaine, cyclobenzaprine, diclofenac, gabapentin, ibuprofen, ketamine, and pentoxifylline into transdermal compositions, two different penetration enhancer mixtures, essential to improve drug solubility due to their high solubilizing power, were selected and used to formulate pain management-loaded transdermal compositions.² Dispersion of hydrophilic drugs in the aqueous phase is conducted by dissolving the drug with a hydrophilic silicone copolyol, phenyl trimethicone, and a non-ionic water-in-oil (W/O) emulsifier with a hydrophile-lipophile balance (HLB) value from about 1 to about 8, polyoxyethylene sorbitan monostearate, to make silicone-in-water-in-oil (S/W/O) emulsions.³ Dispersion of lipophilic drugs in the oil phase is conducted by dissolving the drug with a silicone copolyols with alkyl chains compatible with hydrocarbon oils, alkyl dimethicone, to make W/O emulsions, or with non-ionic oil-in-water (O/W) emulsifier agents with an HLB value from about 8 to about 18, cetostearyl polyoxyethylene ether and ethylene oxide/propylene oxide copolymer to make O/W emulsions.

ABSTRACT

Transdermal compositions for pain management are comprised of nonsteroidal anti-inflammatory drugs, opioid drugs, and adjuvant drugs acting on: voltage-gated channels, gamma-aminobutyric acid receptors, acute musculoskeletal pain, and as an antidepressant. In this work, baclofen, bupivacaine, cyclobenzaprine, diclofenac, gabapentin, ibuprofen, ketamine, and pentoxifylline were loaded in transdermal compositions, prepared using a mixture of lipids (isopropyl palmitate and mineral oil) and one of two selected penetration enhancer mixtures: alkyl dimethicone, phenyl trimethicone, and polyoxyethylene sorbitan monostearate; and cetostearyl polyoxyethylene ether and ethylene oxide/propylene oxide copolymer. The influence of penetration enhancers on transdermal delivery was evaluated using Franz-type diffusion cells and Normal Human 3D Model of Epidermal Tissue. Results showed that drug delivery is affected by the penetration enhancer used in the transdermal composition.

MATERIALS AND METHODS

MATERIALS

The excipients used in the study and their lot numbers and suppliers are listed below:

- Phenyl trimethicone (Dow Corning 556; Dow Corning, Midland, Michigan)
- Alkyl dimethicone (Dow Corning AMS-C30)
- Polyoxyethylene sorbitan monostearate (Simulgel NS; Seppic, Puteaux Cedex, France)
- Cetostearyl polyoxyethylene ether (Procol CS-20-D; Protameen Chemicals, Totowa, New Jersey)
- Ethylene oxide/propylene oxide copolymer (Poloxamer 407; Sigma Aldrich, St. Louis, Missouri)

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The active pharmaceutical ingredients used in the study and their lot numbers and suppliers are listed below:

- Baclofen USP (Lot UWJJK-LO; TCI Chemicals, Portland, Oregon)
- Bupivacaine Hydrochloride USP (Lot 7845H; MP Biomedicals, Santa Ana, California)
- Cyclobenzaprine Hydrochloride USP (Lot LC24561; AK Scientific, Union City, California)
- Diclofenac Na USP (Lot A0325573; Acros Organics, Geel, Belgium)
- Gabapentin USP (Lot E021-103-21A; Shanghai Shaoyuan, Shanghai, China)
- Ibuprofen USP (Lot A0311465; Acros Organics)
- Ketamine Hydrochloride USP (Lot 1CD0165; Spectrum Chemical, New Brunswick, New Jersey)
- Pentoxifylline BP (Lot 7591K; MP Biomedicals, Santa Ana, California)

SAMPLE PREPARATION

Pain management formulations were prepared by mixing an oil phase with a water phase, lipophilic emulsifier phase, and/or a hydrophilic emulsifier phase, using a high-shear mixing method.

Method of Preparation for the Oil Phase

1. Charge kettle with isopropyl palmitate and mineral oil
2. Install mixer.
3. Heat to 75°C to 80°C.
4. Turn on the mixer.

Method of Preparation for the Water Phase

1. Add purified water in tank equipped with mixer.
2. Turn on the mixer.
3. Heat to 75°C to 80°C.

Method of Preparation for the Lipophilic Emulsifier Phase

1. Add either alkyl dimethicone or cetostearyl polyoxyethylene ether and ethylene oxide/propylene oxide copolymer to the oil phase.
2. Add lipophilic actives.
3. Mix until dissolved.

Method of Preparation for the Hydrophilic Emulsifier Phase

1. Add phenyl trimethicone and polyoxyethylene sorbitan monostearate to the oil phase.
2. Add hydrophilic actives
3. Mix until dissolved.

Method of Preparation for the Emulsion Phase

1. Combine the oil phase and water phase in kettle with mixing.
2. Mix for 1 hour.

The advantages of S/W/O emulsions are:

- Excellent spreading and film-forming properties
- Gloss
- Dry non-sticky feel
- Good flow properties even at low temperatures
- Good thermal resistance
- Good oxidative resistance
- Low-surface tension
- Can use larger amounts of hydrophilic or lipophilic active substances without lessening storage stability
- Sustained and controlled release of a wide range of pharmaceutical actives

Dispersion of hydrophilic drugs is conducted by dissolving the drugs with a hydrophilic silicone copolyol, phenyl trimethicone, along with a monomeric surfactant, polyoxyethylene sorbitan monostearate, to make S/W/O emulsions. Hydrophilic drugs have an uptake capacity of about 30% to about 35%.

Dispersion of lipophilic drugs are conducted by dissolving the drugs with silicone copolyols with various alkyl chains compatible with hydrocarbon oils, alkyl dimethicone, to make W/O emulsions. Lipophilic drugs have an uptake capacity of about 30% to about 35%.

EX VIVO SKIN PENETRATION AND PERMEATION STUDIES

Engineered Human Skin (Model EPI-606X; Mattek Corporation, Ashland, Massachusetts) was shipped for delivery on Tuesday morning. Upon receipt of the EpiDerm skin model samples, the sealed plate containing the skin model samples and the assay medium were placed into the refrigerator (4°C). The EpiDerm skin model samples were used as soon as possible. For consistency, all experiments were begun at 8:00 AM on Wednesday morning.

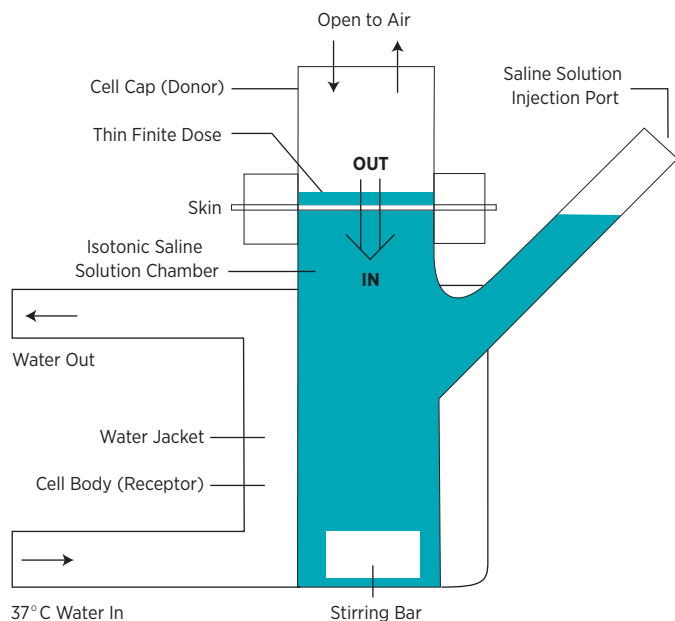
Franz Diffusion System (Model FDC-6; Logan Instruments, Somerset, New Jersey) was used to approximate the permeability of a material through the skin (Figure 1). However, the orifice size of the device determines which EpiDerm model was used as follows:

Orifice Diameter	EpiDerm Model	Usable Tissue Diameter
18 mm	EPI-606X	22 mm

It was necessary that removal of the tissue from the cell culture insert be performed using the following information/instructions:

1. For accurate permeability measurements, the permeant could not simply be added to the cell culture insert since permeant bypass would have occurred at the side wall tissue interface.
2. Using a sharp knife, the sample was removed from the plastic part of the cell culture insert.
3. The resultant disc was then placed stratum corneum side up into the permeation device.
4. It was preferable not to remove the EpiDerm sample from the underlying microporous membrane of the cell culture insert.
5. The underlying membrane did not affect permeability, as it was a highly porous, Teflon-based, chemically inert material.

FIGURE 1. Schematic of permeation device used in the study to approximate the permeability of a material through the skin.



The donor weights were 1.0 gram. Typically, receiver solution concentrations were 1 ppm to 100 ppm versus the donor sample concentrations of 0.1% to 10.0%. Routinely, 12 mL of phosphate buffered saline was used as the receiver solution with the Franz chambers. Samples of the receiver solution were saved for later analysis. In all cases, care was taken to dislodge any air bubbles trapped beneath the tissue since intimate receiver fluid/tissue contact is required to obtain accurate permeability measurements. Prior to placing the donor vehicles atop the EpiDerm samples, the Franz chambers containing the tissues were equilibrated to 37°C for at least 15 minutes. After this period, the permeant vehicle was transferred onto stratum corneum #1 at 8:00 AM, stratum corneum #2 at 8:05 AM, stratum corneum #3 at 8:10 AM, stratum corneum #4 at 8:15 AM, stratum corneum #5 at 8:20 AM, and stratum corneum #6 at 8:25 AM—this marks time 0.0 for the experiment. Multiple data points were taken over this period:

2 hours (Wednesday 10:00 AM – 10:25 AM)
 4 hours (Wednesday 12:00 PM – 12:25 PM)
 8 hours (Wednesday 4:00 PM – 4:25 PM)
 12 hours (Wednesday 8:00 PM – 8:25 PM)
 24 hours (Thursday 8:00 AM – 8:25 AM)
 32 hours (Thursday 4:00 PM – 4:25 PM)
 48 hours (Friday 8:00 AM – 8:25 AM)

At each time point, the entire receiver solution was removed, stored, and replaced with fresh receiver solution. The uniformity of

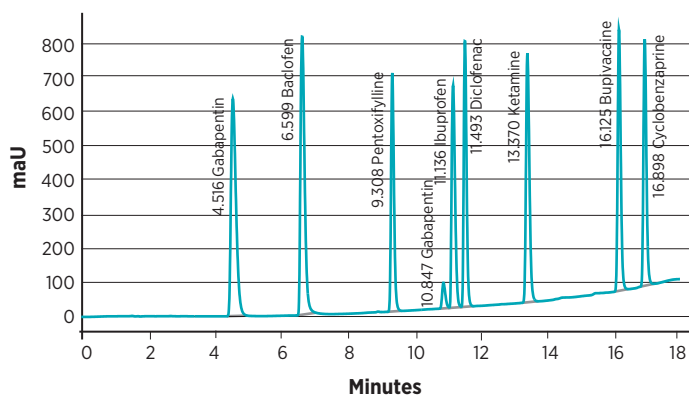
the concentration of the permeant in the receiver solution was insured by using a small magnetic stir bar to mix the receiver solution during the permeability experiment.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

A reverse-phase high-performance liquid chromatographic (HPLC) method was developed which used a pH-buffered phosphate solution and acetonitrile to create a gradient to separate the components of the formulation. A sample chromatogram of gabapentin, baclofen, pentoxifylline, ibuprofen, diclofenac, ketamine, bupivacaine, cyclobenzaprine is shown in Figure 2. The details of the method, including the HPLC instrument conditions and mobile phase preparation, are provided below:

HPLC:	Model 1100; Agilent Technologies, Cedar Creek, Texas	
Column:	Model Gemini C18; Phenomenex, California	
Guard Column:	SecurityGuard C18; Phenomenex	
Temperature:	25°C	
Mobile Phase A:	0.025M Sodium Phosphate Dibasic, pH 3.0 phosphoric acid	
Mobile Phase B:	Acetonitrile	
Gradient Profile:		
Time (Minute)	% A	% B
0	90	10
5	90	10
25	20	80
30	90	10
35	90	10
Flow Rate:	1.0 mL/min	
Injection Volume:	10 µL	
Wavelength:	220 nm	
Seal/Needle Rinse:	50/50 Acetonitrile/Water	
Run Time:	37 minutes	

FIGURE 2. Sample chromatogram of gabapentin, baclofen, pentoxifylline, ibuprofen, diclofenac, ketamine, bupivacaine, and cyclobenzaprine.



STATISTICAL ANALYSIS OF DATA

Data analysis was carried out with the software package Microsoft Excel 2013. Significance was tested at the 0.05 level of probability (*P*).

RESULTS

In this study, we prepared and analyzed transdermal compositions for pain management containing high quantities of different penetration-enhancer mixtures. Indeed, we aimed at investigating penetration-enhancer mixture capability to act as solubilizers and as penetration enhancers for improved transdermal delivery of both hydrophilic and lipophilic drugs. To this end, five different safe, bio-compatible penetration enhancers (i.e., phenyl trimethicone, alkyl dimethicone, polyoxyethylene sorbitan monostearate, cetostearyl polyoxyethylene ether, ethylene oxide/propylene oxide copolymer) largely used in topical preparations were used to formulate penetration enhancer mixtures.

COMPOSITION DESIGN AND CHARACTERIZATION

A preferred embodiment of Composition 1 was comprised of a hydrophilic silicone copolyol in a concentration range of 0.1% to 4.0%; a lipophilic silicone copolyol in a concentration range of 1.0% to 20.0%; an organic W/O emulsifying agent in a concentration range of 1.0% to 20.0% (Table 1).

A preferred embodiment of Composition 2 comprises organic O/W emulsifiers in a concentration range of 1.0% to 20.0% (Table 1).

EX VIVO SKIN PENETRATION AND PERMEATION STUDIES

The skin penetration ability of pain management drugs was probed by ex vivo Franz diffusion studies on Normal Human 3D Model of Epidermal Tissue. The amount of drug accumulated into receptor fluid is expressed as the percentage of the drug applied onto the skin. Both penetration-enhancer mixtures promoted deposition in the receptor fluid. In particular, alkyl dimethicone, phenyl trimethicone, and polyoxyethylene sorbitan monostearate allowed the highest drug accumulation into and through the skin.

DISCUSSION

BACLOFEN

The data indicate that baclofen penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration for 48 hours after dose application of Humco Salt-Stable LS Advanced (Composition 1), and for 8 hours after dose application of Base "A" (Composition 2). Humco Salt-Stable LS Advanced performed significantly better than Base "A" at delivering baclofen through human skin (*P* value = 0.01) (Figure 3).

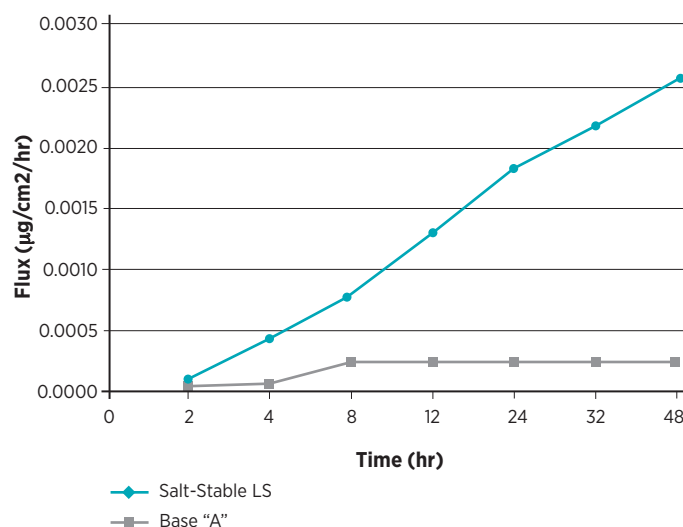
BUPIVACAINE

The data indicate that bupivacaine hydrochloride (HCl) penetrated into and through human epidermal cultures, *in vitro*, from

TABLE 1. Preferred Embodiments of Compositions 1 and 2.

INGREDIENT	COMPOSITION 1 AMOUNT	COMPOSITION 2 AMOUNT
Purified water	55.78% w/w	55.78% w/w
Veegum HS	1.50% w/w	1.50% w/w
Poloxamer 407	-----	4.90% w/w
Simulgel NS	4.90% w/w	-----
Light mineral oil	18.00% w/w	18.00% w/w
Procol CS-20-D	-----	12.50% w/w
Dow Corning AMS-C30	12.50% w/w	-----
Dow Corning 556	2.66% w/w	-----
Lecithin	-----	1.33% w/w
Isopropyl palmitate	-----	1.33% w/w
Aloe vera oil	1.00% w/w	1.00% w/w
Dow Corning 200-350	1.00% w/w	1.00% w/w
Euxyl PE9010	1.00% w/w	1.00% w/w
Germaben II-E	1.00% w/w	1.00% w/w
Vitamin E oil	0.66% w/w	0.66% w/w

FIGURE 3. Baclofen Flux vs. Time.



the test formulations provided. The absorption profiles indicate a steady penetration for 32 hours after dose application of Humco Salt-Stable LS Advanced (Composition 1), and for 12 hours after dose application of Base "A" (Composition 2). Humco Salt-Stable LS Advanced performed significantly better than Base "A" at delivering bupivacaine HCl through human skin (*P* value = 0.32) (Figure 4).

CYCLOBENZAPRINE

The data indicate that cyclobenzaprine HCl penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration for 48 hours after dose application of Humco Salt-Stable LS Advanced (Composition 1), and for 12 hours after dose application of Base "A" (Composition 2). Humco Salt-Stable LS Advanced performed significantly better than Base "A" at delivering cyclobenzaprine HCl through human skin (P value = 0.50) (Figure 5).

DICLOFENAC

The data indicate that diclofenac Na penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration to a peak flux occurring at approximately 24 hours after dose application. Humco Salt-Stable LS Advanced (Composition 1) performed slightly better than Base "A" (Composition 2) at delivering Diclofenac Na through human skin (P value = 0.09) (Figure 6).

FIGURE 4. Bupivacaine Flux vs. Time

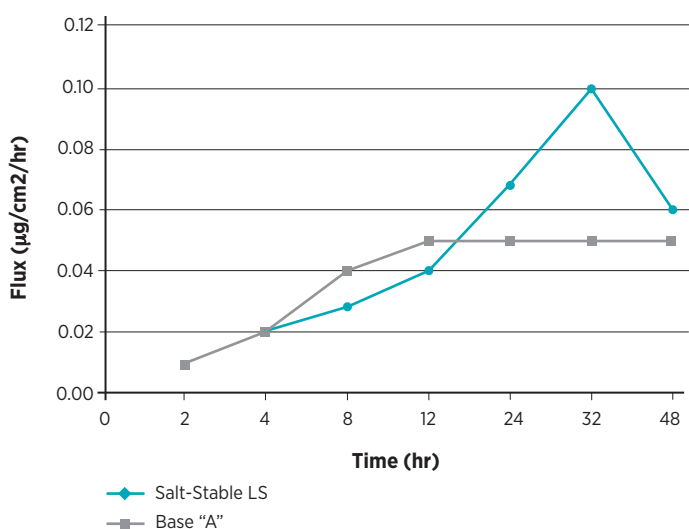


FIGURE 6. Diclofenac Na Flux vs. Time.

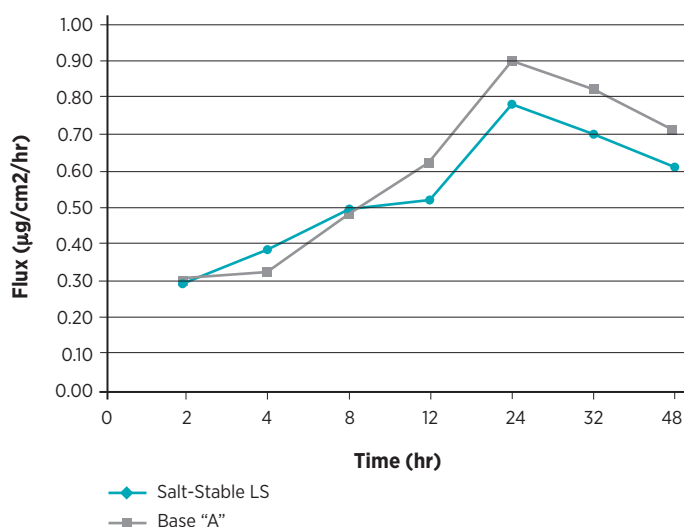
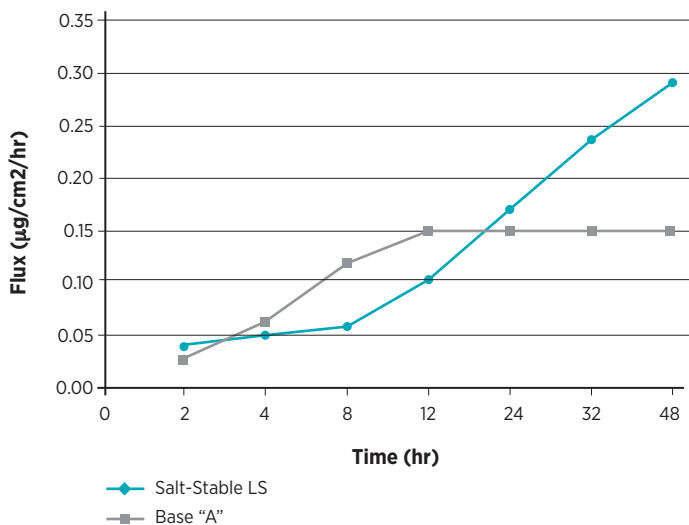


FIGURE 5. Cyclobenzaprine Flux vs. Time.

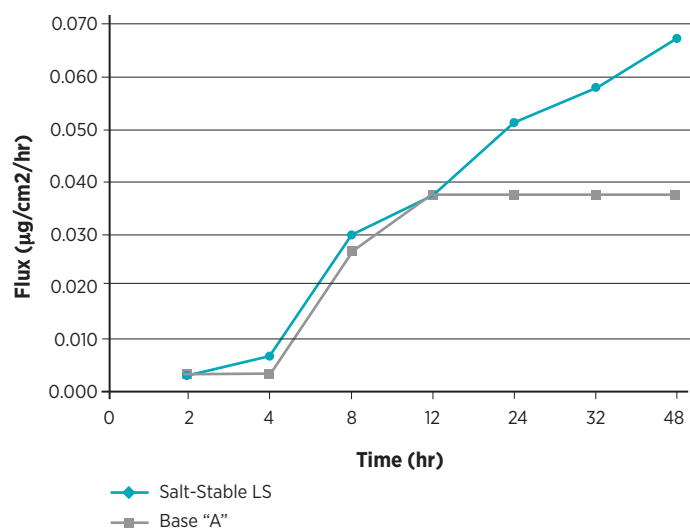
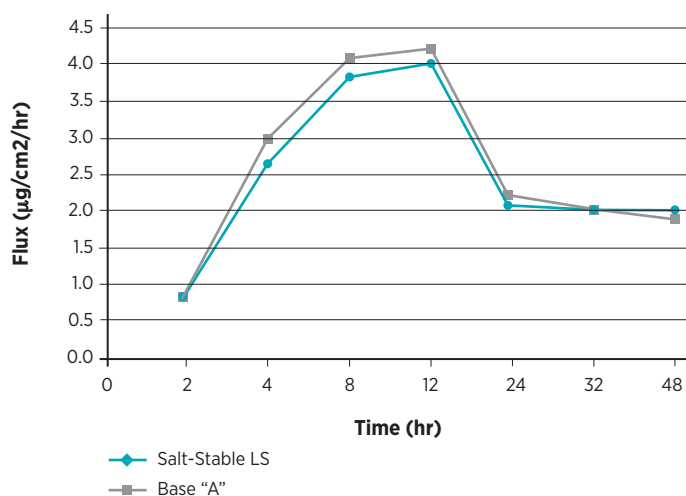
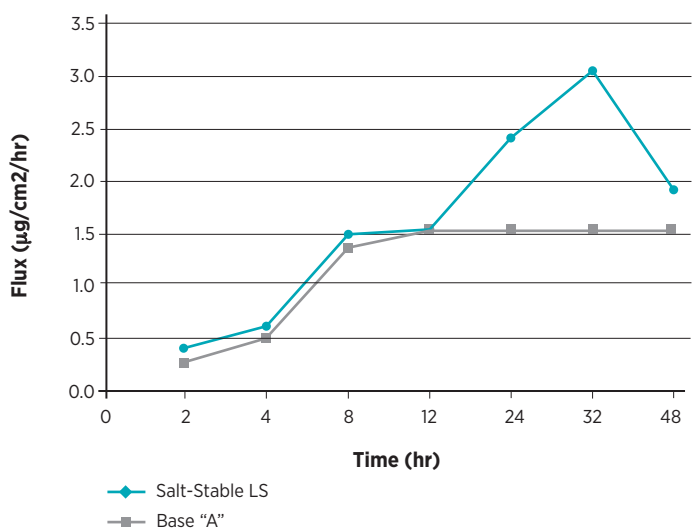
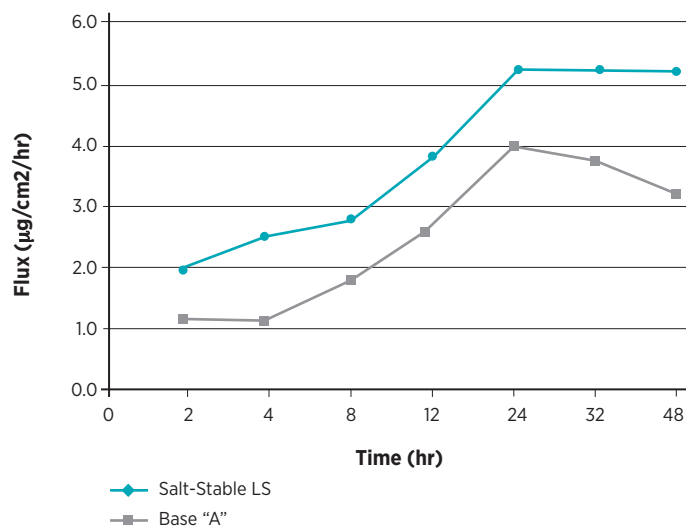


GABAPENTIN

The data indicate that gabapentin penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration for 48 hours after dose application of Humco Salt-Stable LS Advanced (Composition 1), and for 12 hours after dose application of Base "A" (Composition 2). Humco Salt-Stable LS Advanced performed significantly better than Base "A" at delivering Gabapentin through human skin (P value = 0.06) (Figure 7).

IBUPROFEN

The data indicate that ibuprofen penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration for 32 hours after dose application of Humco Salt-Stable LS Advanced (Composition 1), and for 12 hours after dose application of Base

FIGURE 7. Gabapentin Flux vs. Time.**FIGURE 9. Ketamine Flux vs. Time.****FIGURE 8. Ibuprofen vs. Time.****FIGURE 10. Pentoxifylline Flux vs. Time.**

"A" (Composition 2). Humco Salt-Stable LS Advanced performed significantly better than Base "A" at delivering Ibuprofen through human skin (P value = 0.09) (Figure 8).

KETAMINE

The data indicate that ketamine HCl penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration to a peak flux occurring at approximately 12 hours after dose applica-

tion. Humco Salt-Stable LS Advanced (Composition 1) performed slightly better than Base "A" (Composition 2) at delivering ketamine HCl through human skin (P value = 0.14) (Figure 9).

PENTOXIFYLLINE

The data indicate that pentoxifylline penetrated into and through human epidermal cultures, *in vitro*, from the test formulations provided. The absorption profiles indicate a steady penetration to a peak flux occurring at approximately 24 hours after dose application. Humco Salt-Stable LS Advanced (Composition 1) performed

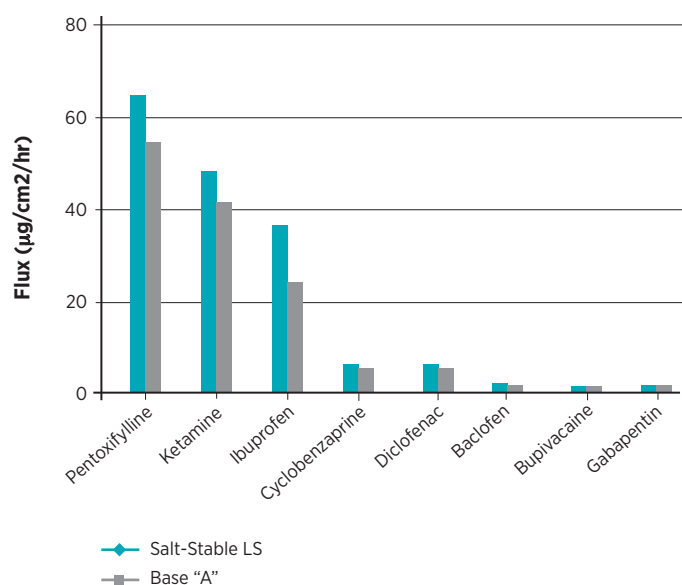
significantly better than Base "A" (Composition 2) at delivering pentoxifylline through human skin (P value = 0.00) (Figure 10).

CONCLUSION

In this study, we used a high amount (15.16%) of hydrophilic penetration enhancers and a high amount (4.90%) of lipophilic penetration enhancers in Composition 1, and a high amount (17.40%) of hydrophilic penetration enhancers in Composition 2, to facilitate pain management drug incorporation into transdermal compositions, and to avoid pain management drug precipitation. Results underline the ability of alkyl dimethicone, phenyl trimethicone, and polyoxyethylene sorbitan monostearate to improve drug solubility in transdermal compositions, but above all, to have a synergic effect as penetration enhancers. The total percent of applied dose that penetrated past the stratum corneum with Humco Salt-Stable LS Advanced (Composition 1) was significantly better than Base "A" (Composition 2) (Figure 11).

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FIGURE 11. Results of penetration enhancers to facilitate pain management drug incorporation into transdermal compositions.



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