The Release and Transdermal Penetration of Baclofen Formulated in a Poloxamer Lecithin Organogel

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INTRODUCTION
Over the past decade there have been an extraordinary number of prescriptions that have been compounded into penetrating-enhancing topical gels using poloxamer lecithin organogel base as the primary vehicle. Although the use of these gels is widespread, few reports in the literature have tested the release and dermal penetration of active ingredients from these delivery systems. Consequently, there is an increasing need for the evaluation of the effective penetration of active ingredients compounded into poloxamer lecithin organogels.

Topical delivery of drugs to the skin provides many advantages over the utilization of other routes of drug delivery. These advantages include: the ability to bypass the first pass effect of the liver on metabolism, reduced side effects, and improved patient compliance. Nevertheless, despite advances in dermatological drug-delivery systems in the last decade, only a few drugs possess suitable physico-chemical and pharmacological properties for optimal topical or transdermal drug delivery. Recently, the incorporation of a variety of active drugs into transdermal gels such as poloxamer lecithin organogel (PLO) has become popular with compounding pharmacists. These preparations are routinely compounded using a variety of different active ingredients. However, there is often relatively little evidence which supports the dermal penetration of such compounds.

ABSTRACT
The purpose of this study was to evaluate the in vitro release and ex vivo penetration of baclofen following incorporation into a 2% poloxamer lecithin organogel. Franz cells were utilized for both the release and penetration studies. Semi-permeable dialysis membranes were used for the release testing, and porcine skin was used as the model skin for the penetration study. Baclofen release and penetration at predetermined time points were assessed using high-performance liquid chromatographic analysis. Results demonstrated that baclofen release from the poloxamer lecithin organogel was significantly higher than its penetration through porcine skin. The amount of baclofen released by the poloxamer lecithin organogel was linear up to 12 hours. Approximately 20% of applied drug was released over the duration of the study period. In comparison with drug released, the ex vivo penetration of baclofen through porcine skin was very low with only minute detectable quantities (significantly less than 1%) after the 12-hour study period. These results suggest that the request to include baclofen into a compounded poloxamer lecithin organogel should be approached cautiously by compounding pharmacists.

The purpose of this study was to evaluate the in vitro release and ex vivo penetration of baclofen following incorporation into a 2% poloxamer lecithin organogel. Baclofen is a gamma-aminobutyric acid derivative and is a centrally acting muscle relaxant. It is a white, odorless, crystalline powder that is slightly soluble in water and very slightly soluble in methanol. Baclofen has a molecular weight of 213.76 and is chemically a zwitterion at neutral pH due to the presence of both amino and carboxylic acid functional groups. Due to close proximity, amino and carboxylic acid groups are able to hydrogen bond, further stabilizing the zwitterionic structure (Figure 1). Baclofen has previously been included in PLO formulations with other drugs for the purposes of treating fibromyalgia and neuropathic pain. Due to its highly charged, zwitterionic nature at neutral pH, however, one would expect that baclofen would not meet the necessary requirements for satisfactory clinical dermal penetration. The purpose of this work was to test that hypothesis in an ex vivo porcine skin model.

MATERIALS AND METHODS
Baclofen USP grade powder (Lot 127K1281) was obtained from Sigma-Aldrich (St. Louis, Missouri). Semi-permeable dialysis tubing used was Spectra/Porous Membrane (Lot 20097) and was purchased from Spectrum (Gardena, California). Potassium phosphate monobasic (Lot 087K0245) and dibasic (Lot 082K0113) were obtained from Sigma-Aldrich.

Figure 1. Chemical structure of baclofen.
Le classiche lesioni associate ad un prodromo, possono emergere da un virus inattivo alloggiato nel gaglio. Quando si scatena, il virus inattivo si riproduce e viaggia lungo il sistema nervoso periferico causando vesciche in specifiche mucose. Le ripetizioni “onde virali” possono aggiungere le lesioni già esistenti. Queste lesioni si può rispondere con una terapia preventiva, come l’esposizione al sole o sostanze anti virali.

Per i trattamenti sintomatici di lesioni classiche e non, ci sono numerose prescrizioni che contrastano le sostanze focalizzate. Generalmente, queste includono agenti con proprietà anestetiche (anestetici locali, antistaminici), antiprurito, antivirali, emollienti e protettivi.

Recentemente il sodio laurilsolfato ha mostrato di migliorare l’efficienza di altre sostanze antivirali quando includono una concentrazione al 5%, presumibilmente per migliorare l’assorbenza delle sostanze antivirali.

La terapia combinata è stata ritenuta benefica. Nel passato, i pazienti erano stati avvisati a non usare i corticosteroide per il trattamento del herpes per sopprimere l’infiammazione che possono causare una grande lesione nella convalescenza. Comunque, una combinazione di un antivirale con un corticosteroide può superare questi problemi.

Il composto antivirale può sopprimere le infezioni interrompendo la replicazione virale e il corticosteroide può accelerare la guarigione e sopprimere l’infiammazione.

La lista della tabella 1 usa sostanze comuni per la prevenzione e il trattamento del herpes con l’uso delle loro forze.

I 3 principali scopi nel trattamento del herpes sono i seguenti:
1. Alleviare il dolore e il fastidio
2. Prevenire infezioni batteriche secondarie.
3. Prevenire la diffusione di altre.
<table>
<thead>
<tr>
<th>Droghe</th>
<th>Quantità usuali</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anestetizzati/antipruriti/antinfiammatori</strong></td>
<td></td>
</tr>
<tr>
<td>Benzocaina</td>
<td>5-20%</td>
</tr>
<tr>
<td>Alcool Benzilico</td>
<td>10-33%</td>
</tr>
<tr>
<td>Canfora</td>
<td>0.1-3%</td>
</tr>
<tr>
<td>Desametasone</td>
<td>0.1%</td>
</tr>
<tr>
<td>Dibucaina</td>
<td>0.25-1%</td>
</tr>
<tr>
<td>Difenidramina cloridrata</td>
<td>1%</td>
</tr>
<tr>
<td>Diclonina cloridrata</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Idrocortisone</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Lidocaina</td>
<td>1-5%</td>
</tr>
<tr>
<td>Mentolo</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Fenolo</td>
<td>1-3%</td>
</tr>
<tr>
<td>Tetracaina</td>
<td>2%</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Antivirale</strong></td>
<td></td>
</tr>
<tr>
<td>Aciclovir</td>
<td>5%</td>
</tr>
<tr>
<td>Deoxy-d glucosio</td>
<td>0.2%</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Orale</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>1%</td>
</tr>
<tr>
<td>Valciclovir</td>
<td>Orale</td>
</tr>
<tr>
<td>Docosanololo</td>
<td>10%</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Iniezione</td>
</tr>
<tr>
<td>Sodio Lauril solfato</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Erbe</strong></td>
<td></td>
</tr>
<tr>
<td>Succo di limone (estratto secco)</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Emollienti</strong></td>
<td></td>
</tr>
<tr>
<td>Allantoina</td>
<td>qs</td>
</tr>
<tr>
<td>Burro di cacao</td>
<td>qs</td>
</tr>
<tr>
<td>Dimeticone</td>
<td>qs</td>
</tr>
<tr>
<td>Glicerina</td>
<td>qs</td>
</tr>
<tr>
<td>Petrolito</td>
<td>qs</td>
</tr>
</tbody>
</table>
Come visto nella tabella 2 ci sono diversi punti da ricordare nel curare l’herpes e dei consigli per il paziente.

<table>
<thead>
<tr>
<th>Tabelle 2: Trattamento generale e consigli per herpes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulire l’area usando un sapone delicato e asciugando con vari colpetti con l’asciugamano disponibile.</td>
</tr>
<tr>
<td>2. Applicare la protezione(emolliente) sulla pelle 4-5 volte al giorno per diminuire la secchezza e tenere le lesioni soffici, diversamente, possono divenire secche e rompersi, risultando così più suscettibile all’infezione</td>
</tr>
<tr>
<td>3. Gli Anestetici topici locali in un solvente emolliente possono diminuire il bruciore, il prurito e il dolore.</td>
</tr>
<tr>
<td>4. Se contagioso, usare una triplice pomata antibiotica, o un antibiotico orale.</td>
</tr>
<tr>
<td>5. Se la lesione persiste più di 14 giorni, contattare il medico</td>
</tr>
<tr>
<td>6. Lavare frequentemente le mani durante il giorno.</td>
</tr>
<tr>
<td>7. Evitare i fattori che possano ritardare i processi di guarigione, come lo stress, traumi locali, vento, luce solare e stanchezza</td>
</tr>
<tr>
<td>8. Se suscettibili al herpes, usare una abituale protezione solare sulle labbra e sulla faccia.</td>
</tr>
<tr>
<td>9. Le lesioni sono contagiose, così minimizzare il contatto con altri e nell’usare cosmetici, ecc.</td>
</tr>
<tr>
<td>10. Il trattamento è sintomatico e diminuirà solo il prurito e il dolore.</td>
</tr>
</tbody>
</table>

Dosaggi di formule usate per curare l’herpes
Le più comuni formule di dosaggi usate per curare l’herpes includono capsule e tavolette orali e topiche. Lo scopo di quest’articolo, sarà limitare la discussione su formule di dosaggio topico.
Il più conveniente dosaggio per questa forma di applicazione potrebbe essere uno stick. Dopo averlo applicato, è meglio se un sottile strato di medicina è rimosso e scartato per prevenire nuove infezioni. Gli stick non dovrebbero mai essere condivisi. Le pomate, le creme e i gel per le labbra sono comunemente usate, in quanto emollienti e relativamente facili da applicare. E’ meglio un salvadito o un applicatore con punta di cotone per rimuovere la pomata o uno stick; una volta usato il paziente lo butta. Ciò minimizza la reinfezione. E’ meglio usare un salvadito per rimuovere la pomata e applicarla alle labbra perché questo può contaminare. Le mani dovrebbero essere completamente pulite prima e dopo l’applicazione.
Le creme e i gel generalmente non hanno “il potere di stare attaccate”della pomata. Esse possono essere preparate, per avere una grande abilità penetrativa per l’attività delle sostanze.
I liquidi topici possono essere usati ma devono contenere entrambi agenti che incrementano la viscosità o la volatilità del solvente così il liquido non si disperde fuori dall’area trattata. Precedentemente il composto di tintura di benzoino era usato nell’herpes come protettivo. I liquidi topici non sono usati molto.
ESEMPI DI FORMULE

STICKS

ACICLOVIR 5%, LIDOCAINA 1% E SODIO LAURIL SOLFATO 5% (BASE SOLUBILE IN ACQUA)

<table>
<thead>
<tr>
<th>Ingredienti</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>5g</td>
</tr>
<tr>
<td>Lidocaina</td>
<td>1g</td>
</tr>
<tr>
<td>Sodio Lauril Solfato</td>
<td>5g</td>
</tr>
<tr>
<td>Polietilenglicole 3350</td>
<td>26g</td>
</tr>
<tr>
<td>Polietilenglicole 300</td>
<td>63g</td>
</tr>
</tbody>
</table>

1. Polverizzare le polveri e miscelarle insieme
2. Sciogliere la base del Peg insieme a 55°C.
3. Incorporare le polveri e miscelarle uniformemente
4. Raffreddare leggermente, e poi inserire le sostanze nello stampo degli stick

ACICLOVIR 5%, LIDOCAINA 1% E SODIO LAURIL SOLFATO 5% (base alcolica-acqua)

<table>
<thead>
<tr>
<th>Ingredienti</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>5g</td>
</tr>
<tr>
<td>Lidocaina</td>
<td>1g</td>
</tr>
<tr>
<td>Sodio Lauril Solfato</td>
<td>5g</td>
</tr>
<tr>
<td>Cera bianca</td>
<td>5g</td>
</tr>
<tr>
<td>Aroma</td>
<td>qs</td>
</tr>
<tr>
<td>Petroli idrofilo</td>
<td></td>
</tr>
<tr>
<td>(Acquafar, Acquabase)</td>
<td>100g</td>
</tr>
</tbody>
</table>

1. Polverizzare le polveri e miscelarle insieme
2. Sciogliere la cera bianca e il petroli idrofilo insieme fino a divenire fluido
3. Incorporare le polveri e miscelarle uniformemente.
4. Raffreddare leggermente, aggiungere l’aroma se desiderato, e poi inserire le sostanze nello stampo degli stick.
### POMATE

#### BALSAMO DI LABBRA EMOLIENTE CON 5% DI BENZOCAINA

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
<th>Uso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaina</td>
<td>5g</td>
<td>Polverizzare le benzocaina e miscelare con l’olio di germe di frumento e l’olio d’oliva.</td>
</tr>
<tr>
<td>Olio di germe di frumento</td>
<td>10g</td>
<td>Usando un basso calore, ammorbidire il burro di cacao e incorporarlo nella miscela di benzocaina, mescolando bene.</td>
</tr>
<tr>
<td>Olio d’oliva</td>
<td>10g</td>
<td>Inserirlo in appropriati contenitori e raffreddare.</td>
</tr>
<tr>
<td>Burro di cacao</td>
<td>75g</td>
<td>Imballare ed etichettare.</td>
</tr>
</tbody>
</table>

1. Polverizzare le benzocaina e miscelare con l’olio di germe di frumento e l’olio d’oliva.
2. Usando un basso calore, ammorbidire il burro di cacao e incorporarlo nella miscela di benzocaina, mescolando bene.
3. Inserirlo in appropriati contenitori e raffreddare.
4. Imballare ed etichettare.

#### POMATE PER FEBBRI

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
<th>Uso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acido tannico</td>
<td>6g</td>
<td>Miscelare la canfora e il fenolo.</td>
</tr>
<tr>
<td>Canfora</td>
<td>9g</td>
<td>Aggiungere la benzocaina seguito dall’acido tannico.</td>
</tr>
<tr>
<td>Fenolo</td>
<td>3g</td>
<td>Aggiungere l’alcool sufficientemente per dissolvere la miscela.</td>
</tr>
<tr>
<td>Benzocaina</td>
<td>2g</td>
<td>Aggiungere lentamente alla soluzione il solvente di petrolito idrofilo e miscelarlo.</td>
</tr>
<tr>
<td>Alcool</td>
<td>qs</td>
<td>Imballare ed etichettare.</td>
</tr>
<tr>
<td>Petrolito idrofilo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Acquabase, acquafor)</td>
<td>100g</td>
<td></td>
</tr>
</tbody>
</table>

1. Miscelare la canfora e il fenolo.
2. Aggiungere la benzocaina seguito dall’acido tannico.
3. Aggiungere l’alcool sufficientemente per dissolvere la miscela.
4. Aggiungere lentamente alla soluzione il solvente di petroilto idrofilo e miscelarlo.
5. Imballare ed etichettare.

#### DEOXY-D-GLUCOSIO 0.2%, LIDOCAINA CLORIDRATO 5%, SODIO LAURIL SOLFATO 5%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
<th>Uso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxy-d-Glucosio</td>
<td>200mg</td>
<td>Polverizzare le polveri e miscelarle insieme.</td>
</tr>
<tr>
<td>Lidocaina cloridrato</td>
<td>5g</td>
<td>Aggiungere il glicole propilenico e formare una pasta liscia.</td>
</tr>
<tr>
<td>Sodio lauril solfato</td>
<td>5g</td>
<td>Incorporare la crema idrofila (Dermabase, Vanicrema, Velvacol) geometricamente e miscelare uniformemente.</td>
</tr>
<tr>
<td>Glicole propilenico</td>
<td>5mL</td>
<td></td>
</tr>
<tr>
<td>Crema idrofila</td>
<td>qs</td>
<td>Imballare ed etichettare.</td>
</tr>
<tr>
<td></td>
<td>100g</td>
<td></td>
</tr>
</tbody>
</table>

1. Polverizzare le polveri e miscelarle insieme.
2. Aggiungere il glicole propilenico e formare una pasta liscia.
3. Incorporare la crema idrofila (Dermabase, Vanicrema, Velvacol) geometricamente e miscelare uniformemente.
4. Imballare ed etichettare.
**CREMA AL BALSAMO DI LIMONE 1%**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balsamo di limone, estratto secco</td>
<td>1g</td>
</tr>
<tr>
<td>Lidocaina cloridrato</td>
<td>5g</td>
</tr>
<tr>
<td>Glicerina</td>
<td>5g</td>
</tr>
<tr>
<td>Crema idrofila</td>
<td></td>
</tr>
<tr>
<td>(Dermabase, Vanicrema)</td>
<td>qs 100g</td>
</tr>
</tbody>
</table>

1. Miscelare l’estratto secco di balsamo di limone, e la lidocaina cloridrata con la glicerina fino a formare una pasta liscia.
2. Incorporare il solvente di crema idrofila e miscelare uniformemente.
3. Imballare ed etichettare.
GELS

GEL TOPICO DI ACICLOVIR 5% E LIDOCAINA CLORIDRATO 2%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>5g</td>
</tr>
<tr>
<td>Lidocaïna cloridrata</td>
<td>2g</td>
</tr>
<tr>
<td>Metilcellulosa</td>
<td>3g</td>
</tr>
<tr>
<td>Metilparabene</td>
<td>100mg</td>
</tr>
<tr>
<td>Propilparabene</td>
<td>50mg</td>
</tr>
<tr>
<td>Acqua distillata</td>
<td>qs 100g</td>
</tr>
</tbody>
</table>

1. Bollire 50ml di acqua distillata.
2. Disperdere il parabene e il metilparabene e miscelare.
3. Aggiungere aciclovir e lidocaïna in 40 mL di acqua conservata.
4. Miscelare le due miscele.
5. Aggiungere l’acqua conservata in modo sufficiente al volume e miscelare.

GEL TOPICO ACICLOVIR 5% E SODIO LAURIL SOLFATO 5%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>5g</td>
</tr>
<tr>
<td>Sodio lauril solfato</td>
<td>5g</td>
</tr>
<tr>
<td>Pluronic F 127</td>
<td>18g</td>
</tr>
<tr>
<td>Acqua purificata</td>
<td>qs 100g</td>
</tr>
</tbody>
</table>

1. Miscelare l’aciclovir e il sodio lauril solfato con 75 mL di acqua distillata.
2. Metterlo in frigo fino a raffreddarlo.
3. Aggiungere il Pluronic F127 e acqua purificata sufficiente al volume e miscelarla.
4. Mettere nel frigo e lasciarlo tutta la notte.
5. Imballare ed etichettare.

GEL TOPICO DI FOSCARNET 3% E SODIO LAURIL SOLFATO 5%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foscarnet</td>
<td>3g</td>
</tr>
<tr>
<td>Sodio lauril solfato</td>
<td>5g</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>18g</td>
</tr>
<tr>
<td>Acqua distillata</td>
<td>qs 100g</td>
</tr>
</tbody>
</table>

1. Miscelare il foscarnet e il sodio lauril solfato con circa 75mL di acqua distillata.
2. Mettere in frigo e raffreddare.
3. Aggiungere il Pluronic F127 e acqua sufficiente al volume e miscelare.
4. Mettere in frigo e lasciare tutta la notte.
5. Imballare ed etichettare.
### GEL TOPICO DI ACICLOVIR 5% E DESAMETASONE 0.1%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>5g</td>
</tr>
<tr>
<td>Desametasone</td>
<td>100mg</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>18g</td>
</tr>
<tr>
<td>Acqua distillata</td>
<td>100g</td>
</tr>
</tbody>
</table>

1. Miscelare l’aciclovir e il desametasone in circa 75 mL di acqua distillata.
2. Aggiungere il Pluronic F127 e acqua sufficiente al volume e miscelare.
3. Mettere in frigo e lasciare tutta la notte.
4. Imballare e etichettare.

### GEL TOPICO DI FOSCARNET 3% E TRIAMCINOLONE ACETATO 0.1%

<table>
<thead>
<tr>
<th>Ingrediente</th>
<th>Quantità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foscarnet</td>
<td>3g</td>
</tr>
<tr>
<td>Triamcinolone acetato</td>
<td>100mg</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>18g</td>
</tr>
<tr>
<td>Acqua distillata</td>
<td>qs</td>
</tr>
</tbody>
</table>

1. Miscelare foscarnet e il triamcinolone acetato con circa 75 mL di acqua distillata.
2. Mettere in frigo e raffreddare.
3. Aggiungere il Pluronic F127 e acqua purificata sufficiente al volume e miscelare.
4. Mettere in frigo e lasciare tutta la notte.
5. Imballare ed etichettare.
L-Arginine and Ascorbic Acid for Diabetic Foot Ulcers

Combination therapy appears to promote healing of diabetic foot ulcers.

One of the many complications of diabetes mellitus is ulceration of the lower extremities. Diabetic foot ulcers are the most common cause of nontraumatic amputations and are responsible for 25% of all diabetic hospitalizations. The cost to the health-care system is great for this seemingly simple occurrence, yet the solution to this problem remains unresolved. Poor blood flow due to vascular endothelial dysfunction is currently considered to be the underlying cause of this condition. L-arginine is converted in the body to nitric oxide, which is a potent vasodilator. It is proposed that supplementation with this amino acid may help increase vascular blood flow to ulcerated areas. Ascorbic acid has also been shown to improve endothelial-dependent vasodilation in diabetic patients. Together these nutrients may aid healing of diabetic foot ulcers.

Physiology

When an injury occurs to the foot of an otherwise healthy individual, the body responds by causing increased blood flow to the area. This increase causes an influx of the components necessary for healing to the injury site. When there is a compromise in this blood flow, altered healing is the result. For the diabetic patient, this often means a chronic ulceration and possible infection. Recent studies have indicated that the diabetic foot ulcer may be due more to neuropathy than to peripheral vascular disease. These studies have shown that a dysfunction in the endothelium of the microvasculature may, in fact, be at the root of this condition.

The endothelium is the single layer of cells lining the vessels. One of its many functions is to release nitric oxide, which causes vasodilation. L-arginine is a naturally occurring substance found in the endothelial cells. Nitric oxide is produced from L-arginine by nitric oxide synthetase and diffuses into the surrounding smooth muscle cells, causing vasodilation. When there is a dysfunction in any of these mechanisms, failure of the microvasculature to dilate may occur.

Topical Treatment of Diabetic Foot Ulcers

It is important to maintain adequate hydration when treating an ulcer. However, care must be taken not to cause excessive moisture to the area surrounding the wound. If there is exposure to bone, cartilage or tendons, moisture is needed to keep cell death from occurring. If the wound is dry due to peripheral artery occlusion, then a hydrating formula may not be appropriate. If the tissue is drying due to environmental exposure, then a hydrating formula is recommended and should be used within the margins of the wound. If an exudate is present, a hydrating formula should not be used until a drying agent has been used. The use of a Pluronic lecithin organogel (PLO) should be restricted to nonulcerated areas to avoid cleaning the area after the gel has been applied. This type of penetrating mixture should be used as a preventive measure or on areas of healthy skin around an ulcer to promote vasodilation. Before any type of topical treatment is applied, the patient must obtain a diagnosis from the doctor to ensure that the proper therapy is given.

Discussion

L-Arginine

L-arginine (MW 174.20, C6H14N4O2) is an essential amino acid and is available in a powdered form. Its use as a vasodilator has been studied. Veves and colleagues, in their study using acetylcholine and sodium nitroprusside, have shown a response in patients with diabetes mellitus and peripheral neuropathy or peripheral vascular disease to nitric oxide release. The response was seen in both the endothelial-dependent (acetylcholine) and the endothelial-independent (sodium nitroprusside) pathways. A greater response, however, was seen in patients who were healthy or had diabetes mellitus alone. While the response to the nitric oxide may be decreased in diseased patients, some therapeutic benefit still remains. L-arginine releases nitric oxide by way of the endothelial-dependent pathway and its mechanism has been tested in several studies.

Ascorbic Acid

Ascorbic acid (MW 176.13, C6H8O6) is available as a white to yellow powder. It is mostly odorless. While relatively stable in air, it will darken upon exposure to light. Its solubility is 1 g to 3 mL water; it is slightly soluble in alcohol. It is often used as an antioxidant. Recent studies have postulated that the reduced response from the endothelial-dependent pathway is due to intracellular scavengers. These scavengers are thought to be produced by cyclooxygenase and can be reduced by ascorbic acid supplementation. This may improve the response to L-arginine and provide an even greater benefit for the patient.

Zinc Sulfate

Zinc sulfate (MW 161.44, ZnSO4) is available as transparent needles or prisms, or as a crystalline powder. It is odorless and has a metallic taste. It effloresces in dry air. It is soluble in water and glycerin and is insoluble in alcohol. It is used as an astringent and antiseptic. When used topically, it increases the rate of healing of skin ulcers.

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Oklahoma City, OK 73118
**Formulations**

**L-ARGININE AND ASCORBIC ACID HYDRATING ULCER GEL**

<table>
<thead>
<tr>
<th>Rx</th>
<th></th>
</tr>
</thead>
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<tr>
<td>L-arginine</td>
<td>10%</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>1.25%</td>
</tr>
<tr>
<td>Zinc sulfate</td>
<td>2%</td>
</tr>
<tr>
<td>Methylcellulose 4000 cps</td>
<td>5%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>0.5%</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.015%</td>
</tr>
<tr>
<td>Purified water qs ad</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Procedure**
1. Calculate the quantity of each required ingredient.
2. Accurately weigh and measure each ingredient.
3. Disperse the methylcellulose in 80 mL of hot water (80 to 90°C).
4. Chill overnight in a refrigerator.
5. Dissolve the L-arginine, ascorbic acid and zinc sulfate in 18 mL of purified water.
6. Dissolve the methylparaben in the propylene glycol.
7. Carefully mix the methylcellulose, active ingredients and propylene glycol fractions to avoid incorporating air.
8. Add sufficient purified water to volume and mix well.

**L-ARGININE AND ASCORBIC ACID IN PLO**

<table>
<thead>
<tr>
<th>Rx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>L-arginine</td>
<td>25%</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>1%</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate liquid</td>
<td>20%</td>
</tr>
<tr>
<td>Pluronic 30% gel qs</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Procedure**
1. Dissolve the L-arginine and ascorbic acid in 50 mL of the Pluronic 30% gel.
2. Add lecithin and isopropyl palmitate liquid and mix well.
3. Minimize incorporation of air.
4. Add sufficient Pluronic 30% gel to volume and mix well.
5. Protect from light.

**Methylcellulose**

Methylcellulose is available as white powder or granules. It is stable in alkalis or weak acids. It is neutral in aqueous suspensions. It is insoluble in alcohol and is soluble in glacial acetic acid. Some of its uses include as a dispersing, thickening and emulsifying agent.

**Propylene Glycol**

Propylene glycol (MW 76.10, C₃H₈O₂) is a clear, viscous liquid. It is practically odorless with a slight acrid taste. It has a specific gravity of 1.035 to 1.037. It is hygroscopic in moist air. It is miscible with water and alcohol and is soluble in ether. It will dissolve many volatile oils but is immiscible with fixed oils. It is used as a solvent, preservative and humectant.

**Methylparaben**

Methylparaben (MW 152.15, C₈H₈O₃) is a clear crystal or white powder. It has almost no odor and a burning taste. It is soluble in ethanol, water, glycerin and propylene glycol. It has a melting point of 125 to 128°C. It is used for its antimicrobial properties at a pH between 4 and 8. It is most active against molds, yeasts and gram-positive bacteria. Some ulcer patients may be sensitive to parabens; if allergy develops, use should be discontinued.

**Purified Water**

Purified water is prepared from potable water by a process of reverse osmosis, distillation, ion exchange or another method. It is used as the basis for many compounded formulations.

**Poloxamers**

Poloxamers (Pluronics) are nonionic copolymers used as emulsifiers; gelling, spreading, wetting and stabilizing agents; tablet coatings and suppository bases. Their solubility varies depending on the poloxamer type, but all are freely soluble in ethanol and water. Poloxamers are stable in acids and alkalis; however, they do not support mold growth. They are available as white, waxy granules and are odorless and tasteless.

**Lecithin**

Lecithin is a naturally occurring phospholipid. It comprises two fatty acids, one glycerol and phosphoric acid molecule and a nitrogenous base such as choline. It is used as an emulsifier and an-
oxidant. Lecithin oxidizes rapidly in air and will darken.9

Isopropyl Palmitate

Isopropyl palmitate (MW 298.51, C<sub>19</sub>H<sub>38</sub>O<sub>2</sub>) is available as a clear to pale yellow liquid. It is viscous in nature and will solidify at 16°C. It is very stable to hydrolysis and oxidation. It is soluble in ethanol, mineral oil and hydrocarbon; and it is insoluble in glycerin and water. It is used in detergents, soaps, perfumes and various topical preparations.15

Conclusion

The use of an appropriate topical dressing in the treatment of diabetic foot ulcers can accelerate healing. While further controlled studies are needed to determine the complete benefit from L-arginine and ascorbic acid, sufficient data exist to imply benefit to the diabetic patient.

References


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Other reagents used were 99.99% acetonitrile (Lot 00549ED) and 99.99% methanol (Lot 08865LD), both of which were purchased from Sigma-Aldrich and were high-performance liquid chromatographic (HPLC) analytical- or special reagent-grade commercial products.

**COMPOUNDING OF PLO**

The formulation for the 2% baclofen PLO vehicle was obtained from an established recipe and is outlined herein. The lecithinisopropyl palmitate solution (Lot WM3170; Spectrum Chemicals, Gardena, California) contained 0.2 grams of sorbic acid and 49.9 grams of soy lecithin in 40.0 grams of isopropyl palmitate. The mixture was stirred for 5 minutes using a hand-held blender and was stored at room temperature for 8 hours until complete dissolution was obtained. The gel contained 20 grams of Pluronic F-127, 0.2 grams of potassium sorbate, and sufficient purified water to make 100 grams of gel. The container was sealed and placed in a refrigerator overnight until complete dissolution.

To compound the baclofen PLO, the syringe-to-syringe method was utilized. Briefly, the baclofen was added to the lumen of a syringe and 6 mL of ethyl alcohol was added. The mixture was agitated until the baclofen was completely dissolved. Next, 22 mL of the lecithin solution was added, and the formulation was mixed. In a separate syringe, the Pluronic F-127 was added and the two syringes were connected; the formulation was mixed back and forth between both syringes until the preparation thickened.

**IN VITRO RELEASE OF BACLOFEN FROM GEL**

Modified Franz diffusion cells (Permegear Inc., Riegelsville, Pennsylvania) were used for the evaluation of baclofen release (diffusional area of 0.64 cm², the receptor volume 5.1 mL) (Figure 2). The receptor was filled with isotonic phosphate buffer (pH 7.2) and maintained at 37°C ± 0.5°C, and continuously stirred at 600 rpm. Four- to five-inch sections of semi-permeable dialysis tubing were soaked in room temperature water for 12 hours. Dialysis tubing was cut and placed on top of each Franz diffusion cell and approximately 500 mg of gel was placed on top of the dialysis tubing. Samples of 300 mcL each were taken over a 12-hour time course. The volume of each sample was replaced with the same amount of buffer solution. The samples were immediately transferred to a refrigerator with a temperature setting of 5°C and were stored until they were quantitatively analyzed.

**TRANSDERMAL PENETRATION STUDY**

Porcine skin was the skin model utilized for this transdermal study. Modified Franz diffusion cells were used for the evaluation of baclofen transdermal penetration through porcine skin (diffusional area of 0.64 cm², the receptor volume 5.1 mL). The receptor was filled with isotonic phosphate buffer (pH 7.2) and maintained at 37°C ± 0.5°C, and continuously stirred at 600 rpm. Porcine skin was obtained from a local abattoir mounted on top of the Franz cells and allowed to equilibrate for 30 minutes. After equilibration, approximately 500 mg of gel was placed on each skin. Samples of 300 mcL each were taken over a 12-hour time course. The volume of each sample was replaced with the same amount of buffer solution. The samples were immediately transferred to a refrigerator with a temperature setting of 5°C and were stored until they were quantitatively analyzed.

**ANALYTICAL METHODOLOGY**

Quantitative analysis of baclofen was conducted using a Breeze Chromatography Manager Windows-based system, a Waters 1525 Binary HPLC Pump (Serial #L0025P; Waters Corporation, Milford, Massachusetts), a Waters 717 Plus auto injector/auto sampler (Serial #MX6NM37533M; Waters Corporation), a Waters dual absorbance UV detector (Serial #007487105R; Waters Corporation) set at 220-nm, and a reversed phase C8 analytical column (Spherisorb, 150 X 4.6 mm (millimeter) ID, 5 mcµm (Lot 52943-04; Supelco, St. Louis, Missouri). The mobile phase consisted of potassium phosphate (0.1 M) buffer plus methanol plus acetonitrile at a ratio of 85:10:5, respectively, at a pH of 2.5. The mobile phase solution was mixed thoroughly and degassed with a Waters In-Line Degasser (Serial #M001LD; Waters Corporation) and was used with a flow rate of 1.2 mL per minute at ambient temperature. Sharp, well-resolved peaks were obtained at a retention time of 6.1 minutes. Standard preparation solutions consisted of Baclofen USP for final concentrations of 0.0001, 0.01, 0.1, and 1 mg/mL, which were prepared by serial dilution. Standard and assay preparations were obtained in triplicates. Samples were run for 8 minutes with an injection volume of 10 mcL. The squared correlation coefficients for the standard curve (0.0001 to 0.1 mg/mL) was >0.999 (r²).

**RESULTS**

The results for the in vitro release and ex vivo penetration of baclofen are presented in Figures 3 and 4, respectively. Initially, the release rate of baclofen was tested through incubation of 500 mg of the 2% gel (approximately 10 mg of active ingredient) in Franz cells donor chambers above a semi-permeable dialysis membrane. Time-dependent appearance in the receiver chamber was then measured. In vitro release of baclofen from the PLO vehicle was linear for the duration of the 12-hour study period (Figure 3). Approximately 20% (1.98 ± 0.35 mg) of the baclofen was released throughout the duration of the in vitro study. Subsequently, an ex vivo study was conducted in which porcine skin replaced...
the semi-permeable dialysis membrane and the same amount of the 2% baclofen PLO was placed in the donor chamber (Figure 4). At the end of the 12-hour study period only about 0.22% (0.022 ± 0.015 mg) of the incubated baclofen had penetrated the porcine skin. These data indicate an approximately 90-fold reduction in porcine skin penetration versus release from the PLO formulation.

**DISCUSSION**

PLO has gained wide acceptance in the pharmaceutical compounding community as a popular vehicle for the dermal and transdermal delivery of drugs. Many have assumed that PLO would provide a suitable and effective means for delivering a variety of compounds. Nevertheless, despite the ability of PLO to disrupt skin and enhance drug penetration, physiochemical characteristics of the drug itself such as molecular size, hydrophilic/lipophilic balance, and charge are critical in determining the ultimate penetration of the drug compound. This is especially important to remember when deciding whether the drug to be included is an appropriate candidate for inclusion in a PLO vehicle.

Baclofen, a centrally-acting muscle relaxant, has been purported to be effective in the treatment of neuropathic pain and fibromyalgia. Despite the ability of PLO to disrupt skin and enhance drug penetration, other peripheral ailments through topical administration is unclear. Baclofen has traditionally been thought to act primarily in the central nervous system by inhibiting the transmission of both monosynaptic and polysynaptic reflexes at the level of the spinal cord through a gamma-aminobutyric acid pathway. Others have suggested that baclofen could have a depressant effect on N-methyl-D-aspartate receptors found in peripheral musculature. Nonetheless, whether acting centrally or peripherally, adequate penetration of the baclofen is required.

Based on physiochemical properties, a minimal penetration of baclofen in the absence of any disruption of the skin’s barrier function would be expected. Baclofen exists as a zwitterion at physiological pH with a charged amine and carboxylic acid group (Figure 1). In fact, baclofen has been proposed to be absorbed orally by an active amino acid transport route and was shown to not be absorbed following rectal administration. However, the effect that an absorption enhancing gel such as PLO could have on the transdermal penetration of a drug like baclofen in PLOs is the opinion of the authors that because of low release rates and extremely low transdermal permeation rates, the compounding of baclofen into PLOs should be approached with caution. Furthermore, more studies are needed to evaluate the dermal penetration of compounds from PLOs.

**CONCLUSION**

In the presented study, a baclofen PLO was compounded and release rates and transdermal permeation were determined using pig skin. It is the opinion of the authors that because of low release rates and extremely low transdermal permeation rates, the compounding of baclofen into PLOs should be approached with caution. Furthermore, more studies are needed to evaluate the dermal penetration of compounds from PLOs.

**REFERENCES**


Address correspondence to John Arnold, PhD, McWhorter School of Pharmacy, Samford University, 800 Lakeshore Drive, Birmingham, AL 35229. E-mail: jarnold@samford.edu
Acido 5 aminolevulinico 10% in gel di Poloxamer

A titolo di esempio, lo sviluppo di un cosiddetto termogel può essere menzionato come base per una formulazione magistrale per uso topico di acido 5-aminolevulinico (5-ALA). Il 5-ALA, viene usato in combinazione con fototerapia per la terapia fotodinamica del melanoma della pelle sono la preparazione con questo p.a. è in genere problematica, perché 5-ALA, è un aminoacido polare, sia per l’assorbimento cutaneo sia per la stabilità chimica.

Veicolato con un termogel, si ha una penetrazione 10 - 25 volte migliore di basi note di farmacopea (Unguento idrofilo DAB, Crema anifila DAC) e di varie specialità commerciali. Ciò è dovuto alla speciale combinazione del gel, costituito da dimetil-isosorbide, alcol isopropilico, trigliceridi a catena media, poloxamer e acqua in composizione quantitativa definita (vedi riquadro).

La formulazione è relativamente facile da allestire. A causa della stabilità chimica limitata di 5-ALA, il p.a. dovrebbe essere aggiunto poco prima dell'uso. Per la termoreversibilità della preparazione, la formulazione è liquida a temperatura di frigorifero, mentre assume consistenza cremosa sopra i 12 °C. Ciò assicura che la formulazione può essere facilmente applicata sulla pelle da trattare.

5-Aminolevulinic 10,0 g
Poloxamer 407 (Pluronic F127) 18,90 g
Alcool isopropilico 11,25 g
Dimetilisosorbide 11,25 g
Trigliceridi a media catena 4,5 g
Acqua 45,0 g

Pesare tutti i componenti in adatto recipiente (Topitec o Unguator)
L'acqua deve essere fredda di frigo. Far girare a 1450 giri per un minuto e mezzo con Topitec o Citounguator, a temperatura ambiente.
E’ anche possibile incorporare il p.a. dopo aver preparato il gel.
Clonidine Hydrochloride 0.2%, Gabapentin 6%, and Ketamine Hydrochloride 10% in a Pluronic Lecithin Organogel (PLO)

**Rx**

For 100 mL
Clonidine hydrochloride 200 mg
Gabapentin 6 g
Ketamine hydrochloride 10 g
Propylene glycol 10 mL
Lecithin:isopropyl palmitate solution 22 mL
Pluronic F127 20% gel qs 100 mL

**METHOD OF PREPARATION**

**Note:** The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 50 g of soy lecithin, and 50 g of isopropyl palmitate. The Pluronic F127 solution can be prepared by mixing 0.2 g potassium sorbate, 20 g of Pluronic F127, and sufficient purified water to make 100 mL.

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Mix the powders together.
4. Add the propylene glycol and mix to form a smooth paste.
5. Add the lecithin:isopropyl palmitate solution and mix well.
6. Add the Pluronic F127 20% gel to volume and use a mechanical shearing force to mix thoroughly.
7. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

Use only as directed. Keep out of reach of children.

**STABILITY**

No stability studies have been conducted on this specific formulation.

**USE**

The formulation is a general combination that can be used when treatment for neuropathic pain is initiated.

**QUALITY CONTROL**

Final yield versus theoretical yield, physical observation.

**DISCUSSION**

Clonidine hydrochloride (C9H9Cl2N3.HCl, MW 266.6) is a centrally α2-adrenergic agonist that occurs as a white or almost white crystalline powder. It is soluble 1 g in 13 mL of water and in dehydrated alcohol. It is slightly soluble in chloroform.1,2

Gabapentin (C9H17NO2, MW 171.2) is an antiepileptic agent that occurs as a white to off-white crystalline solid that is freely soluble in water and in basic or acidic aqueous solutions. It is available as Neurontin capsules, which also contain lactose, cornstarch, and talc.1,3

Ketamine hydrochloride (C13H16ClNO.HCl, MW 274.2) is used as an anesthetic and analgesic. It occurs as a white crystalline powder with a slight characteristic odor. Approximately 1.15 mg is equivalent to 1 mg of ketamine base. It is soluble 1 g in 4 mL of water, in 14 mL of alcohol, in 60 mL of absolute alcohol, and in 60 mL of chloroform.1,2

Propylene glycol (C3H8O2) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste resembling that of glycerin. It has a specific gravity of 1.038 g/mL and is miscible with each of the following: acetone, chloroform, 95% ethanol, glycerin, and water. It is not miscible with fixed oils or light mineral oil. It will, however, dissolve some essential oils. Propylene glycol is actually a better solvent than glycerin. It is similar to ethanol as an antiseptic and is also used in cosmetics and in the food industry as a vehicle for flavors and emulsifiers. It is stable and may be mixed with numerous other solvents. Because propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.4

Lecithin is partially soluble in water but will hydrate to form emulsions. It is used as an emulsifying and solubilizing agent.5

Isopropyl palmitate is a colorless, mobile liquid with a very slight odor. It is soluble in alcohol and is insoluble in water, in glycerin, and in propylene glycol.6

Pluronic F127 is usually available in powdered form. It is odorless or may have a mild odor. It melts at about 56°C and is freely soluble in water, in alcohol, and in isopropyl alcohol.7

The patient should be advised that as the preparation is rubbed onto the skin and becomes warm, it may become slightly more viscous and resistant to rubbing.

**References**

## Chlorhexidine 2% Gel

### Rx

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine diacetate</td>
<td>2 g</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>30 g</td>
</tr>
<tr>
<td>Poloxamer F-127</td>
<td>22 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>qs 100 g</td>
</tr>
</tbody>
</table>

### METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the chlorhexidine diacetate in the propylene glycol at 70°C.
4. Maintain the heat and slowly add, with stirring, the poloxamer F-127 and purified water to weight.
5. Mix thoroughly and maintain the temperature until the air bubbles escape, resulting in a clear, colorless gel.
6. Package and label.

### PACKAGING

Package in tight, light-resistant containers.¹

### LABELING

Keep out of reach of children. Use only as directed. For external use only.

### STABILITY

A beyond-use date of up to 6 months can be used for this preparation.¹

### USE

Chlorhexidine 2% Gel is used in the treatment of susceptible infections.

### QUALITY CONTROL

Quality-control assessment can include theoretical weight compared to actual weight, pH, specific gravity, active drug assay, color, clarity, texture-surface, texture-spatula spread, appearance, feel, rheological properties, and physical observations.²

### DISCUSSION

Chlorhexidine diacetate \((C_{22}H_{30}Cl_{2}N_{10}.2C_{2}H_{4}O_{2}, \text{MW 625.64})\) occurs as a white or almost white, microcrystalline powder. It melts at 154°C and is soluble 1 in 15 of 95% ethanol and 1 in 55 of water and slightly soluble in glycerin and propylene glycol. Aqueous solutions may be sterilized by autoclaving. Chlorhexidine is a bisguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of gram-negative and especially gram-positive bacteria. It is effective against some species of *Pseudomonas* and *Proteus*. It is effective against some viruses and fungi but is inactive against bacterial spores. It is most active at a neutral or slightly acid pH. Combination of chlorhexidine with cetrimide or an alcoholic solution will enhance its efficacy. It is used topically in antiseptic creams, mouthwashes, and dental gels, and in urology for catheter sterilization and bladder irrigation; also as a constituent of medicated dressings, dusting powders, sprays, and creams. Chlorhexidine salts are cationic in solution and are therefore incompatible with soaps and other anionic materials. Other substances that are incompatible include acacia, sodium alginate, sodium carboxymethylcellulose, starch, and tragacanth, as well as brilliant green, chloramphenicol, copper sulfate, fluorescein sodium, formaldehyde, silver nitrate, and zinc sulfate.³

Propylene glycol \((C_{3}H_{8}O_{2}, \text{MW 76.09})\) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste, somewhat resembling glycerin. It has a specific gravity of 1.038 g/mL and is miscible with acetone, chloroform, 95% ethanol, glycerin, and water. It is not miscible with fixed oils or light mineral oil. Propylene glycol is actually a better solvent than glycerin. It is similar to ethanol as an antiseptic and is also used in cosmetics and in the food industry as a vehicle for flavors and for emulsifiers. It is stable and may be mixed with numerous other solvents.⁴

Poloxamers are a series of closely related block copolymers of ethylene oxide and propylene oxide that are used as emulsifying agents, solubilizing agents, and wetting agents. They are available in different grades, either liquids or solids, with average molecular weights ranging from 2,090 to 14,600. Poloxamers generally occur as white-colored, waxy, free-flowing granules or as cast solids that are practically odorless and tasteless. Poloxamer 407 (Pluronic F-127) is generally available in powdered form. It is odorless or may have a very mild odor. It is freely soluble in water, alcohol, or isopropyl alcohol.⁵

Purified water is water that is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, and steam).⁶

### REFERENCES

**Dehydroepiandrosterone 25 mg/mL in Pluronic Lecithin Organogel**

**Rx**

For 100 mL

- Dehydroepiandrosterone: 2.5 g
- Propylene glycol: 1 mL
- Lecithin:isopropyl palmitate solution: 20 g
- Pluronic F127 20% gel: qs to 100 mL

---

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Prepare a paste of the dehydroepiandrosterone in the propylene glycol.
4. Add the lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F127 20% gel to volume and mix well.
6. Package and label.

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

For external use only. Use only as directed.

**STABILITY**

A beyond-use date of 30 days can be used for this formulation.

**USE**

Dehydroepiandrosterone Pluronic lecithin organogel has been used for hormonal supplementation.

**QUALITY CONTROL**

Quality control assessment can include weight and/or volume, pH, specific gravity, active drug assay, color, clarity, texture-surface, rheologic properties, and physical observation.

**DISCUSSION**

Dehydroepiandrosterone (C₁₉H₃₀O₂, MW 288.4) is a naturally occurring, relatively weak androgen. It has been commercially available and marketed in several countries. The role of dehydroepiandrosterone in adrenal insufficiency has been studied, and it is a precursor to androgens in hormone replacement therapy.

Propylene glycol (C₃H₈O₂) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste resembling that of glycerin. It has a specific gravity of 1.038 g/mL and is miscible with each of the following: acetone, chloroform, 95% ethanol, glycerin, and water. Because propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) is a complex mixture of acetone-insoluble phosphatides consisting primarily of phosphatidylecholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol in combination with triglycerides, fatty acids, and carbohydrates. The composition and physical properties of lecithin vary depending on the source and degree of purification. Lecithin derived from vegetable sources has a bland or nut-like taste and varies in color from brown to light yellow, depending on whether it is bleached or unbleached. Lecithin is practically insoluble in water, in polar solvents, and in cold vegetable and animal oils; however, when mixed with water, it hydrates to form emulsions. It is soluble in aliphatic and aromatic hydrocarbons, in mineral oil, and in fatty acids. Lecithin decomposes at extremes of pH, is hygroscopic, and is subject to microbial degradation. It should be stored in well-closed containers and protected from light.

Isopropyl palmitate (C₁₉H₃₈O₂, MW 298.51) is a colorless mobile liquid with a very slight odor. It is used as an emollient, an oleaginous vehicle, and a solvent and has good spreading characteristics. It is soluble in each of the following: acetone, castor oil, cottonseed oil, alcohol, and mineral oil. Isopropyl palmitate is insoluble in water, in glycerin, and in propylene glycol. It should be stored in well-closed containers and protected from light.

Poloxamer 407 (Pluronic F127) is usually available in powdered form. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, in alcohol, and in isopropyl alcohol. The pH of a 2.5% w/v aqueous solution of Pluronic F127 is in the range of 6.0 to 7.4. Poloxamers are stable, and their aqueous solutions are stable in the presence of acids, alkalis, and metal ions (although they do support mold growth).

**References**

Cyclobenzaprine Hydrochloride 0.5% and Diclofenac Sodium 3% in Pluronic Lecithin Organogel

**Rx**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine hydrochloride</td>
<td>500 mg</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>3 g</td>
</tr>
<tr>
<td>Ethoxy diglycol</td>
<td>10 mL</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate solution</td>
<td>22 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% gel</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the cyclobenzaprine hydrochloride and diclofenac together and mix with the ethoxy diglycol.
4. Incorporate the mixture into about 70 mL of the Pluronic F-127 gel and mix well.
5. Incorporate the lecithin and isopropyl palmitate solution and mix well using a high-shear mixing method.
6. Incorporate sufficient Pluronic F-127 20% gel to volume and continue mixing using a high-shear mixing method.
7. Package and label.

**PACKAGING**

Package in a tight, light-resistant container.¹

**LABELING**

For external use only. Use only as directed. Keep out of reach of children.

**STABILITY**

A beyond-use date of up to 30 days is appropriate for this preparation.¹

**USE**

Cyclobenzaprine and diclofenac in Pluronic lecithin organogel has been used in the treatment of pain of various origin.²

**QUALITY CONTROL**

Quality control tests can include theoretical weight compared to actual weight, specific gravity, active drug assay, rheological properties, and physical observations.²

**DISCUSSION**

Cyclobenzaprine hydrochloride (C₂₀H₂₁N·HCl, MW 311.85) occurs as a white to off-white, odorless, crystalline powder that is freely soluble in water and in alcohol; it is sparingly soluble in isopropanol.¹

Diclofenac sodium (C₁₄H₁₀Cl₂NNaO₂, MW 318.13) is a phenylacetic acid derivative that is a nonsteroidal anti-inflammatory agent with antipyretic activity. It is used in the treatment of inflammatory diseases (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis), dysmenorrhea, and for its antipyretic effect. It is used topically in the treatment of actinic keratoses as a 3% gel. It occurs as a white to off-white, hygroscopic, crystalline powder. It is soluble in ethanol and sparingly soluble in water. It should be preserved in tight, light-resistant containers.¹,³

Ethoxy diglycol (C₅H₈O₂, CH₂OHCH₂OCH₂CH₂OC₂H₅, MW 134.20, diethylene glycol monoethyl ether, diethylene glycol ethyl ether, Carbitol, Transcutol). It occurs as a colorless liquid with a mild pleasant odor. It is hygroscopic and is miscible with water and with common organic solvents. It has a density of 1.0272 and a boiling point of 195°C to 202°C and is combustible. It is nonirritating and nonpenetrating when applied to human skin and is used as a solvent, solubilizer, and cosurfactant.⁴

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex derived from vegetable sources. Lecithin is practically insoluble in water, polar solvents, and cold vegetable and animal oils; when mixed with water, it hydrates to form emulsions. It should be stored in well-closed containers protected from light.¹,⁵

Isopropyl palmitate (C₃₉H₇₈O₂, MW 298.51) is a colorless, mobile liquid that is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol. It should be stored in well-closed containers and protected from light.¹,⁶

Pluronic F-127 (Poloxamer 407) is generally available in powdered form. It is either odorless or may have a very mild odor. It is freely soluble in water, alcohol, and isopropyl alcohol.¹,⁷

**REFERENCES**


---

**For 100 mL**

Note: The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 50 g of soy lecithin and 50 g of isopropyl palmitate. The Pluronic F-127 solution can be prepared by mixing 0.2 g sorbic acid, 20 g of Pluronic F-127, and sufficient purified water to make 100 mL.

Note: When counseling the patient concerning this preparation, it is advisable to explain its temperature-dependent viscosity. As the preparation is rubbed into the skin and warms up, it may become slightly more viscous and resistant to rubbing.
Cyclobenzaprine Hydrochloride 0.5% and Diclofenac Sodium 3% in Pluronic Lecithin Organogel

<table>
<thead>
<tr>
<th></th>
<th>For 100 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine hydrochloride</td>
<td>500 mg</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>3 g</td>
</tr>
<tr>
<td>Ethoxy diglycol</td>
<td>10 mL</td>
</tr>
<tr>
<td>Lecithin and isopropyl palmitate solution</td>
<td>22 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% gel</td>
<td>qs 100 mL</td>
</tr>
</tbody>
</table>

**Note:** The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 50 g of soy lecithin and 50 g of isopropyl palmitate. The Pluronic F-127 solution can be prepared by mixing 0.2 g sorbic acid, 20 g of Pluronic F-127, and sufficient purified water to make 100 mL.

**METHOD OF PREPARATION**
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the cyclobenzaprine hydrochloride and diclofenac together and mix with the ethoxy diglycol.
4. Incorporate the mixture into about 70 mL of the Pluronic F-127 gel and mix well.
5. Incorporate the lecithin and isopropyl palmitate solution and mix well using a high-shear mixing method.
6. Incorporate sufficient Pluronic F-127 20% gel to volume and continue mixing using a high-shear mixing method.
7. Package and label.

**PACKAGING**
Package in a tight, light-resistant container.

**LABELING**
For external use only. Use only as directed. Keep out of reach of children.

**STABILITY**
A beyond-use date of up to 30 days is appropriate for this preparation.

**USE**
Cyclobenzaprine and diclofenac in Pluronic lecithin organogel has been used in the treatment of pain of various origin.

**QUALITY CONTROL**
Quality control tests can include theoretical weight compared to actual weight, specific gravity, active drug assay, rheological properties, and physical observations.

**DISCUSSION**
Cyclobenzaprine hydrochloride (C_{20}H_{21}N.HCl, MW 311.85) occurs as a white to off-white, odorless, crystalline powder that is freely soluble in water and in alcohol; it is sparingly soluble in isopropanol.

**Diclofenac sodium** (C_{13}H_{12}ClNO_{2}, MW 318.13) is a phenylacetic acid derivative that is a nonsteroidal anti-inflammatory agent with antipyretic activity. It is used in the treatment of inflammatory diseases (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis), dysmenorrhea, and for its antipyretic effect. It is used topically in the treatment of actinic keratoses as a 3% gel. It occurs as a white to off-white, hygroscopic, crystalline powder. It is soluble in ethanol and sparingly soluble in water. It should be preserved in tight, light-resistant containers.

**Ethoxy diglycol** (C_{6}H_{14}O_{3}, CH_{2}OHCH_{2}OCH_{2}CH_{1}OC_{2}H_{5}, MW 134.20, diethylene glycol monoethyl ether, diethylene glycol ethyl ether, Carbitol, Transcutol) occurs as a colorless liquid with a mild pleasant odor. It is hygroscopic and is miscible with water and with common organic solvents. It has a density of 1.0272 and a boiling point of 195°C to 202°C and is combustible. It is nonirritating and nonpenetrating when applied to human skin and is used as a solvent, solubilizer, and cosurfactant.

**Lecithin** (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex derived from vegetable sources. Lecithin is practically insoluble in water, polar solvents, and cold vegetable and animal oils; when mixed with water, it hydrates to form emulsions. It should be stored in well-closed containers protected from light.

**Isopropyl palmitate** (C_{18}H_{36}O_{2}, MW 298.51) is a colorless, mobile liquid that is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol. It should be stored in well-closed containers and protected from light.

**Pluronic F-127** (Poloxamer 407) is generally available in powdered form. It is either odorless or may have a very mild odor. It is freely soluble in water, alcohol, and isopropanol.

**REFERENCES**
Diltiazem 2% in Pluronic Lecithin Organogel

Rx

For 100 mL
Diltiazem 2 g
Propylene glycol 5 mL
Lecithin:isopropyl palmitate (1:1) solution 22 mL
Pluronic 20% solution qs 100 mL

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Mix the diltiazem with the propylene glycol to form a smooth paste.
4. Incorporate the lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic 20% solution and mix using a shear action method until uniform.
6. Package and label.

PACKAGING
Package in tight, light-resistant containers.¹

LABELING
Keep out of reach of children. Use only as directed. For external use only.

Note: When counseling a patient concerning this preparation it is advisable to explain its temperature-dependent viscosity. As the preparation is rubbed into the skin and warms up, it may become slightly more viscous and resistant to rubbing.

STABILITY
A beyond-use date of 30 days would be appropriate for this preparation.¹

USE
Diltiazem in Pluronic lecithin organogel has been used in the treatment of wounds by application to the intact skin surrounding the wound.

QUALITY CONTROL
Quality-control assessment can include theoretical weight compared to actual weight, specific gravity, active drug assay, color, texture-surface, texture-spatula spread, appearance, feel, rheological properties and physical observations.²

DISCUSSION
Diltiazem hydrochloride has been used in the treatment of anal fissures.³⁻⁶ Its application to topical wounds is more recent, and it is generally applied to the skin immediately adjacent to the wound area.

Diltiazem hydrochloride (C₂₂H₂₆N₂O₄S.HCl, MW 450.98) is a benzothiazepine-derivative calcium-channel blocker. It occurs as a white, odorless, crystalline powder or as small crystals. It is freely soluble in water and is sparingly soluble in dehydrated alcohol. It melts with some decomposition at about 210°C.¹

Propylene glycol (C₃H₆O₂, MW 76.09) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste somewhat resembling glycerin. It has a specific gravity of 1.038 g/mL and is miscible with 95% ethanol, glycerin and water.⁷

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatidies. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending upon whether bleached or unbleached. Lecithin is practically insoluble in water, polar solvents and cold vegetable and animal oils; however, when mixed with water it hydrates to form emulsions. Lecithin should be stored in well-closed containers and be protected from light.⁸

Isopropyl palmitate (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol and mineral oil.⁹

Pluronic 20% solution is a poloxamer. Poloxamers occur as white-colored, waxy, free-flowing granules or as cast solids that are practically odorless and tasteless. Poloxamer 407 (Pluronic F-127) is generally available in powdered form. It is freely soluble in water, alcohol and isopropyl alcohol.¹⁰

REFERENCES
Estradiol 1-mg/0.1-mL Pluronic Lecithin Organogel

Rx

For 100 mL
Estradiol 1 g
Propylene glycol 1 mL
Lecithin:isopropyl palmitate solutiona 20 g
Pluronic F127 20% gelb qs 100 mL

a The lecithin:isopropyl palmitate solution can be prepared by mixing 10 g of soy lecithin and 10 g of isopropyl palmitate; allow the mixture to stand overnight for complete dissolution to occur.
b The Pluronic F127 20% solution can be prepared by adding 20 g of Pluronic F127 to sufficient cold (ice) water to make 100 mL. To facilitate complete dissolution, place the mixture in a refrigerator, agitate it periodically, and allow it to set.

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Prepare a paste of the estradiol in the propylene glycol.
4. Add the lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F127 20% gel to volume and mix well.
6. Package and label.

PACKAGING
Package in tight, light-resistant containers.

LABELING
For external use only. Use only as directed.

STABILITY
A beyond-use date of 30 days can be used for this formulation.1

USE
Estradiol Pluronic lecithin organogel is used in bioidentical hormone replacement therapy.

QUALITY CONTROL
Quality control assessment can include weight and/or volume, pH, specific gravity, active drug assay, color, clarity, texture-surface, rheologic properties, and physical observation.2

DISCUSSION
Estradiol, a naturally occurring steroidal estrogen, is indicated in the treatment of mild–to-severe vasomotor symptoms associated with menopause.3–5 It occurs as white or creamy white small crystals or as a crystalline powder. It is odorless and hygroscopic and is practically insoluble in water but has a solubility of about 35.7 mg/mL in alcohol at 25°C. Estradiol should be stored in tight, light-resistant containers.

Propylene glycol \((\text{C}_3\text{H}_8\text{O}_2)\) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste resembling that of glycerin. It has a specific gravity of 1.038 g/mL and is miscible with each of the following: acetone, chloroform, 95% ethanol, glycerin, and water. Because propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.6

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatides consisting primarily of phosphatidylethanolamine, phosphatidylserine, and phosphatidylcholine in combination with triglycerides, fatty acids, and carbohydrates. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending on whether it is bleached or unbleached. It is practically insoluble in water, in polar solvents, and in cold vegetable and animal oils. It is soluble in aliphatic and aromatic hydrocarbons, in mineral oil, and in fatty acids. Lecithin should be stored in well-closed containers and protected from light.7

Isopropyl palmitate \((\text{C}_{19}\text{H}_{38}\text{O}_2, \text{MW 298.51})\) is a colorless, mobile liquid with a very slight odor. It is used as an emollient, an oleaginous vehicle, and a solvent and has good spreading characteristics. Isopropyl palmitate is soluble in each of the following: acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, in glycerin, and in propylene glycol. It should be stored in well-closed containers and protected from light.8

Poloxamer 407 (Pluronic F127) is usually available in powdered form. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, in alcohol, and in isopropyl alcohol. The pH of a 2.5% w/v aqueous solution of Pluronic F127 is in the range of 6.0 to 7.4. The poloxamers are stable, and their aqueous solutions are stable in the presence of acids, alkalis, and metal ions but do support mold growth.9

References
Estriol 0.2 mg/0.1 mL in Pluronic Lecithin Organogel

<table>
<thead>
<tr>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estriol, micronized</td>
</tr>
<tr>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Lecithin:isopropyl palmitate solution</td>
</tr>
<tr>
<td>Pluronic® F-127 20% gel</td>
</tr>
</tbody>
</table>

METHOD OF PREPARATION

Note: The lecithin:isopropyl palmitate solution can be prepared by mixing 10 g of soy lecithin and 10 g of isopropyl palmitate; allow to stand overnight for complete dissolution to occur. The Pluronic F-127 20% solution can be prepared by adding 20 g of pluronic F-127 to sufficient cold (ice) water to make 100 mL. For complete dissolution, place in a refrigerator and allow to set, with periodic agitation.

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Prepare a paste of the micronized estriol and the propylene glycol.
4. Add the lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F-127 20% gel to volume and mix well.
6. Package and label.

PACKAGING

Package in tight, light-resistant containers.

LABELING

For external use only. Use only as directed. Store in a refrigerator.

STABILITY

A beyond-use date of 30 days can be used for this formulation.

DISCUSSION

Topically applied estriol is one means of providing natural hormone replacement therapy for patients who prefer an easy-to-apply dosage form. It may be necessary to adjust the estriol concentration or the actual quantity applied for optimum response by the patient. When counseling the patient concerning this preparation, it is advisable to explain its temperature-dependent viscosity. As the preparation is rubbed into the skin and warms up, it may become slightly more viscous and resistant to rubbing.

Estriol is a naturally occurring estrogen and is claimed to have a selective action on the cervix, vagina and vulva and to have relatively little effect on the endometrium. It is often given in combination with estrone and estradiol in estrogen replacement therapy. It is a crystalline powder that is practically insoluble in water but is soluble in alcohol and vegetable oils. In the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol.

Propylene glycol (C₃H₈O₂) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste, somewhat resembling glycerin. It has a specific gravity of 1.038 g/mL and is miscible with acetone, chloroform, 95% ethanol, glycerin and water. Since propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.

Lecithin (egg, soybean or vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatides, consisting chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylvinositol, in combination with triglycerides, fatty acids and carbohydrates. The composition and physical properties vary depending upon the source of the lecithin and the degree of purification. Lecithin is used as an emollient, emulsifying agent and solubilizing agent in topicals, inhalation aerosols, parenterals and oral suspensions. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending upon whether it is bleached or unbleached. It is practically insoluble in water, polar solvents and cold vegetable and animal oils; when mixed with water, though, it hydrates to form emulsions. It is soluble in aliphatic and aromatic hydrocarbons, mineral oil and fatty acids. It will decompose at extremes of pH, is hygroscopic and is subject to microbial degradation. It should be stored in well-closed containers and protected from light.

Isopropyl palmitate (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle and solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol and mineral oil. It is insoluble in water, glycerin and propylene glycol. It should be stored in well-closed containers and protected from light.

Poloxamer 407 (Pluronic F-127) is generally available in powdered form. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, alcohol and isopropyl alcohol. The pH of a 2.5% w/v aqueous solution is in the range of 6.0 to 7.4. The poloxamers are stable and aqueous solutions are stable in the presence of acids, alkalis and metal ions; but the aqueous solutions do support mold growth.

References

Fentanyl 100 µg/0.1 mL in a Pluronic Lecithin Organogel (PLO)

**Rx**

For 100 mL

- Fentanyl citrate 157 µg (equivalent to 100 µg fentanyl)
- Purified water 2 mL
- Lecithin:isopropyl palmitate 22 mL
- Pluronic F127 20% gel qs 100 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Dissolve the fentanyl citrate in the purified water.
4. Incorporate this solution into about 60 mL of the Pluronic F127 20% gel.
5. Incorporate the lecithin:isopropyl palmitate mixture and mix the ingredients well.
6. Add sufficient Pluronic F127 20% gel to volume and mix well.
7. Package and label.

*Note: The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 50 g of soy lecithin, and 50 g of isopropyl palmitate. The Pluronic F127 solution can be prepared by mixing 0.2 g sorbic acid, 20 g of Pluronic F-127, and sufficient purified water to make 100 mL.*

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

For external use only. Use only as directed. Keep out of the reach of children.

**STABILITY**

A beyond-use date of 6 months can be used for this preparation.

**USE**

Fentanyl Pluronic lecithin organogel (PLO) is used in the treatment of moderate-to-severe pain, especially in hospice patients.

**QUALITY CONTROL**

Actual versus theoretical yield, physical appearance.

**DISCUSSION**

Fentanyl citrate in a PLO is frequently used to help relieve pain and nausea. It usually provides pain relief for up to about 6 to 8 hours, and this dosage form can be easily titrated to make the patient more comfortable.

Fentanyl citrate (C_{22}H_{28}N_2O.C_6H_8O_7, MW 528.6) occurs as white granules or as a white crystalline powder. Fentanyl citrate 157 µg is approximately equal to 100 µg of fentanyl. It is soluble 1 g in 40 mL of water and is slightly soluble in alcohol. The pH of the fentanyl injection is in the range of pH 4.0 to 7.5. Fentanyl citrate is a synthetic opioid analgesic used as a sedative, an analgesic, a preoperative medication, and an adjunct to general or regional anesthesia, as well as in the management of chronic pain.

**Purified water** is obtained by distillation, ion exchange, reverse osmosis, or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C, and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid, and steam).

**Lecithin** varies somewhat depending on its origin. Its color may range from light yellow to brown, depending on its source, crop variants, and whether it has been bleached. It is usually odorless but may have a nut-like odor and a bland taste. It is used as an emulsifying and a solubilizing agent.

**Isopropyl palmitate** is a colorless, mobile liquid with a very slight odor. It is soluble in each of the following: acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, in glycerin, and in propylene glycol.

**Pluronic F127** is usually available in powdered form. It is odorless or may have a mild odor. It melts at about 56°C and is freely soluble in water, in alcohol, and in isopropyl alcohol.

**Sorbic acid** (C_{6}H_{8}O_{2}, MW 112.13) is used as an antimicrobial preservative. It is a tasteless, white to yellow-white crystalline powder that has a faint, characteristic odor. It melts at 134.5°C and is soluble 1 g in 400 mL of water at 30°C, in 8 mL of ethanol, in 10 mL of 95% ethanol, in 320 mL of glycerin, and in 19 mL of propylene glycol.

**References**

Formulations

### Glutathione 25% in Pluronic Lecithin Organogel Gel

**Rx**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione, L-reduced</td>
<td>25 g</td>
</tr>
<tr>
<td>Ethoxydiglycol</td>
<td>10 mL</td>
</tr>
<tr>
<td>Soy lecithin:isopropyl palmitate</td>
<td>22 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% gel</td>
<td>qs</td>
</tr>
</tbody>
</table>

**For 100 mL**

**Note:** When counseling the patient concerning this preparation it is advisable to explain its temperature-dependent viscosity. As the preparation is rubbed into the skin and warms up, it may become slightly more viscous and resistant to rubbing.

### METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the ethoxydiglycol with the glutathione to form a smooth paste.
4. Incorporate the soy lecithin:isopropyl palmitate solution and mix well.
5. Incorporate the Pluronic F-127 20% gel geometrically and mix using a shear-mixing method until uniform.
6. Package in syringes that can be used to accurately measure a dose.
7. Label.

### PACKAGING

Package in syringes that are tight and light-resistant and can be used to accurately measure a dose.¹

### LABELING

Keep out of reach of children. Use only as directed. NOT for injection. For external use only.

### STABILITY

A beyond-use date of 14 days can be used for this preparation.¹

### USE

This preparation has been used in the treatment of autism.

### QUALITY CONTROL

Quality-control assessment can include theoretical weight compared to actual weight, specific gravity, active drug assay, color, texture-surface, texture-spatula spread, appearance, feel, rheological properties, and physical observations.²

### DISCUSSION

Glutathione has been used in many different dosage forms in the treatment of autism, including transdermals, troches, etc.

Glutathione (C₅H₇N₂O₅S, MW 307.3) occurs as a white or almost white, crystalline powder or colorless crystals that are freely soluble in water and very slightly soluble in alcohol. It should be protected from light. It is an endogenous peptide with antioxidant and other metabolic functions. It has been used in the treatment of antineoplastic toxicity, various lung disorders, and in heavy metal poisoning, liver disorders, corneal disorders, and eczema.³

**Ethoxydiglycol** (C₆H₁₄O₃, MW 134.20) is also called diethylene glycol monoethyl ether, carbital, and Transcutol. It occurs as a colorless liquid with a mild pleasant odor. It is hygroscopic and is miscible with water and with common organic solvents. It has a density of 1.0272, a boiling point of 195°C to 202°C, and is combustible. It is nonirritating and nonpenetrating when applied to human skin and is used as a solvent, solubilizer, and cosurfactant.⁴

**Soy lecithin** (soybean lecithin, vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatides in combination with triglycerides, fatty acids, and carbohydrates. Lecithin is used as an emollient, emulsifying agent, and solubilizing agent in topicals, inhalation aerosols, parenterals, and in oral suspensions. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending upon whether they are bleached or unbleached. Physically, it ranges from viscous semi-liquids to powders and is practically insoluble in water, polar solvents, and cold vegetable and animal oils; when mixed with water they hydrate to form emulsions.⁵

**Isopropyl palmitate** (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle, and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol.⁶

**Pluronic F-127 20% gel** (poloxamer) is a poloxamer, which are a series of closely related block copolymers of ethylene oxide and propylene oxide that are used as emulsifying agents, solubilizing agents, and wetting agents. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, alcohol, and isopropyl alcohol.⁷

### REFERENCES

Indomethacin 2% in Pluronic-Lecithin Organogel

**Recipe (Rx)**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>2 g</td>
</tr>
<tr>
<td>Ethoxy diglycol</td>
<td>5 mL</td>
</tr>
<tr>
<td>Lecithin and Isopropyl palmitate solution</td>
<td>22 mL</td>
</tr>
<tr>
<td>Pluronic F-127 20% Gel</td>
<td>qs</td>
</tr>
</tbody>
</table>

For 100 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the indomethacin with the ethoxy diglycol.
4. Incorporate the mixture into about 70 mL of the Pluronic F-127 gel and mix well.
5. Incorporate the lecithin and isopropyl palmitate solution and mix well using a high-shear mixing method.
6. Incorporate sufficient Pluronic F-127 20% gel to volume and continue mixing using a high-shear mixing method.
7. Package and label.

**PACKAGING**

Package in a tight, light-resistant container.¹

**LABELING**

For external use only. Use only as directed. Keep out of reach of children.

**STABILITY**

A beyond-use date of up to 30 days is appropriate for this preparation.¹

**USE**

Indomethacin in Pluronic lecithin organogel has been used in the treatment of various skeletal and muscular inflammatory disorders.

**QUALITY CONTROL**

Quality control tests can include theoretical weight compared to actual weight, specific gravity, active drug assay, rheological properties, and physical observations.²

**DISCUSSION**

Indomethacin (C₁₉H₁₄ClNO₄, MW 357.79, Indocin) is a prototypical NSAID that also exhibits analgesic and antipyretic activity. It is primarily used orally or rectally but is also effective when applied topically in a penetrating vehicle. It occurs as a pale yellow-to-yellow–tan, crystalline polymorphic powder with no more than a slight odor. It is sensitive to light and melts at about 162°C. It is practically insoluble in water and sparingly soluble in alcohol.¹ ³

**Ethoxy diglycol** (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid with a very slight odor. It is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol.⁶

**Pluronic F-127** (poloxamer 407) is part of a series of closely related block copolymers of ethylene oxide and propylene oxide available in different grades, either liquids or solids with average molecular weights ranging from 2,090 to 14,600. Poloxamers generally are white-colored, waxy, free flowing granules or as cast solids that are practically odorless and tasteless. Pluronic F-127 is generally available in powdered form. It is either odorless or may have a very mild odor. It is freely soluble in water, alcohol, and isopropyl alcohol.⁷

**REFERENCES**

Ketoprofen 10% in Pluronic Lecithin Organogel

**Rx**

For 100 mL
Ketoprofen 10 g
Propylene glycol 10 mL
Lecithin and isopropyl palmitate solution 22 mL
Pluronic F127 20% gel qs 100 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Mix the ketoprofen and propylene glycol to form a smooth paste.
4. Incorporate the lecithin and isopropyl palmitate solution and mix well.
5. Incorporate sufficient Pluronic F127 20% gel to volume and mix with a high-shear mixing method.
6. Package and label.

**PACKAGING**

Package in a tight, light-resistant container.

**LABELING**

For external use only. Use only as directed.

**STABILITY**

A beyond-use date of 14 days can be used for this preparation.¹

**USE**

Ketoprofen in Pluronic lecithin organogel has been used in the treatment of arthritis and joint and muscular pain in humans and animals.

**QUALITY CONTROL**

Theoretical weight compared with actual weight, pH, specific gravity, active drug assay, color, clarity, texture-surface, texture-spatula spread, appearance, feel, rheological properties, physical observations.²

**DISCUSSION**

Ketoprofen has been administered by numerous routes to many different small and large animal species.¹⁶

Ketoprofen (C₁₆H₁₄O₃, MW 254.28) occurs as a white or almost white, odorless or almost odorless, crystalline powder. It is practically insoluble in water but is freely soluble in alcohol and in ether. Ketoprofen has analgesic, anti-inflammatory, and antipyretic properties and is an inhibitor of cyclo-oxygenase. It should be preserved in tight containers.¹⁷

Propylene glycol (C₃H₈O₂) occurs as a clear, colorless, viscous, practically odorless liquid. It is miscible with acetone, chloroform, 95% ethanol, glycerin, and water. Since propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.⁸

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex derived from vegetable sources. Lecithin is practically insoluble in water, in polar solvents, and in cold vegetable and animal oils; when mixed with water, though, it hydrates to form emulsions. It is soluble in aliphatic and aromatic hydrocarbons, in mineral oil, and in fatty acids. It should be stored in well-closed containers and protected from light.⁹

Isopropyl palmitate (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid that is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, in glycerin, and in propylene glycol. It is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in well-closed containers and protected from light.¹⁰

Pluronic F127 (Poloxamer 407) is usually available in powdered form. It is odorless or may have a very mild odor. It is freely soluble in water, in alcohol, and in isopropyl alcohol.¹¹

Note: It is advisable to explain the temperature-dependent viscosity of this preparation to the patient. As the preparation is rubbed into the skin and warms up, it may become slightly more viscous and resistant to rubbing.

**References**

Lidocaine 10% Oral Pluronic Lecithin Organogel

Rx

<table>
<thead>
<tr>
<th>For 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llidocaine</td>
</tr>
<tr>
<td>Ethoxydiglycol</td>
</tr>
<tr>
<td>Sodium metabisulfité</td>
</tr>
<tr>
<td>Saccharin sodium</td>
</tr>
<tr>
<td>Stevia powder</td>
</tr>
<tr>
<td>Simethicone</td>
</tr>
<tr>
<td>Lecithin:isopropyl palmitate solution</td>
</tr>
<tr>
<td>Puron F-127 20% gel</td>
</tr>
</tbody>
</table>

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the powders with the ethoxydiglycol to form a smooth paste.
4. Incorporate the powder mixture into the lecithin:isopropyl palmitate solution and mix well.
5. Incorporate the Puron F-127 20% gel and mix using a shear technique.
6. Incorporate the simethicone and mix well.
7. Package and label.

PACKAGING
Package in tight, light-resistant containers.1

LABELING
Keep out of reach of children. Use only as directed.

STABILITY
A beyond-use date of up to 30 days can be used for this preparation.3

USE
Lidocaine 10% oral Pluronic lecithin organogel has been used in the treatment of pain and discomfort in the oral cavity.

QUALITY CONTROL
Quality-control assessment can include theoretical weight compared to actual weight, pH, specific gravity, active drug assay, color, texture-surface, texture-spatula spread, appearance, feel, rheological properties, and physical observations.2

DISCUSSION
Lidocaine \((C_{14}H_{22}N_2O, MW 234.34, \text{Lignocaine})\) occurs as a white to slightly yellow crystalline powder with a characteristic odor. It is practically insoluble in water and is very soluble in alcohol; it dissolves in oils.3

Ethoxydiglycol \((C_6H_{14}O_3, CH_2OHCH_2OCH_2CH_2OC_2H_5, MW 134.20)\) is also called diethylene glycol monoethyl ether, diethylene glycol ethyl ether, Carbitol, and Transcutol. It occurs as a colorless liquid with a very slight odor that is used as an emollient, oleaginous vehicle, and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol.3

Simethicone \(\{CH_3[Si(CH_3)2O]nSi(CH_3)3, \text{dimethyl silicone fluid, dimethicone, poly(dimethylsiloxane)}\}\) is a fluid silicone that occurs as a clear colorless, odorless liquid that is insoluble in water and alcohol. It is water-repellent and has a low surface tension.3

Sodium metabisulfité \((Na_2S_2O_5, MW 190.10, \text{disodium disulfite})\) is an antioxidant occurring as colorless, prismatic crystals, or as a white to creamy-white crystalline powder. It is soluble 1 g in 1.9 mL of water, slightly soluble in 95% ethanol, and freely soluble in glycerin.3

Saccharin sodium \((C_{19}H_{38}O_2, MW 298.51)\) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle, and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol.3

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture of which the physical properties vary depending upon the source of the lecithin and the degree of purification.6

Isopropyl palmitate \((C_{19}H_{38}O_2, MW 298.51)\) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle, and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, glycerin, and propylene glycol.9

Puron F-127 20% gel (poloxamer 407) is a poloxamer, which is generally white-colored, waxy, free-flowing granules or as a cast solid that is practically odorless and tasteless. Puron F-127 20% gel is freely soluble in water, alcohol, and isopropyl alcohol.10

REFERENCES
**Methimazole 5 mg/0.1 mL in Pluronic Lecithin Organogel**

**Rx**

(For 3 mL)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methimazole</td>
<td>150 mg</td>
</tr>
<tr>
<td>Lecithin/isopropyl palmitate solution</td>
<td>0.66 mL</td>
</tr>
<tr>
<td>Pluronic F127 gel 20% qs</td>
<td>3 mL</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Use a 3 mL Luer-Lok syringe (or appropriate size depending on the quantity to be prepared; remove the plunger and attach a tip cap).
4. Pour the methimazole powder carefully into the barrel.
5. Add the lecithin/isopropyl palmitate solution and replace the plunger.
6. In a second syringe, measure 2 mL of the Pluronic F127 gel.
7. Attach a Luer-Lok/Luer-Lok adapter to fit the two syringes together and mix the contents back and forth between the syringes.
8. Carefully (do not entrap air), force all the preparation into one syringe and measure the volume.
9. Remove the other syringe and obtain sufficient Pluronic F127 gel to increase the amount of the preparation to volume.
10. Reattach the syringes together and mix the preparation back and forth until it is thoroughly mixed.

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

Use only as directed. Keep out of reach of children.

**STABILITY**

No stability studies have been reported on this preparation. The USP provides a beyond-use date of 14 days when stored in a refrigerator.

**DISCUSSION**

Methimazole is the drug of choice in the treatment of feline hyperthyroid disease. It is more potent and safer than propylthiouracil. The topical Pluronic lecithin organogel (PLO) gel presented here is an alternative to the compounding of an orally administered preparation.

Methimazole occurs as a white-to-pale buff, crystalline powder with a faint, characteristic odor. It is freely soluble in water and in alcohol. It should be stored in a light-resistant container. It is commercially available as 5 and 10 mg tablets.

The poloxamers are a series of closely related block copolymers of ethylene oxide and propylene oxide that are used as emulsifying, solubilizing, and wetting agents. They are available in different grades in either liquids or solids. Average molecular weights range from 2090 to 14,600. Poloxamers usually are white-colored, waxy, free-flowing granules or cast solids that are practically odorless and tasteless. The pH of a 2.5% w/v aqueous solution is in the range of 6.0 to 7.4. The poloxamers are stable, and aqueous solutions are stable in the presence of acids, alkalis, and metal ions; however, the aqueous solutions do support mold growth. Poloxamer 407 (Pluronic F127) is usually available in powdered form. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, in alcohol, and in isopropyl alcohol.

Note: *When the caregiver is counseled about this preparation, its temperature-dependent viscosity should be explained. As the preparation is rubbed into the skin and warms, it may become slightly more viscous and resistant to rubbing.*

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture consisting chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidyserine, and phosphatidylinositol in combination with triglycerides, fatty acids, and carbohydrates. The composition and physical properties vary depending on the source of the lecithin and the degree of purification. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending on whether the source is bleached or unbleached. Physically, the lecithins range from viscous semiliquids to powders. They are practically insoluble in water, in polar solvents, and in cold vegetable and animal oils. When mixed with water, they hydrate to form emulsions. They are soluble in aliphatic and aromatic hydrocarbons, in mineral oil, and in fatty acids. They will decompose at extremes of pH, are hygroscopic, and are subject to microbial degradation. They should be stored in a well-closed container and should be protected from light.

Isopropyl palmitate (C<sub>19</sub>H<sub>38</sub>O<sub>2</sub>, MW 298.51) is a colorless, mobile liquid with a very slight odor that is used as an emollient, an oleaginous vehicle, and a solvent. It has good spreading characteristics. It is soluble in each of the following: acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, in glycerin, and in propylene glycol. It is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container and should be protected from light.

**References**

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh/measure each ingredient.
3. Mix the piroxicam powder with the lecithin:isopropyl palmitate solution until thoroughly dispersed.
4. Add the Pluronic F-127 solution (cold) and mix well.
5. Package and label.

Note: The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 50 g of soy lecithin and 50 g of isopropyl palmitate. The pluronic F-127 solution can be prepared by mixing 0.2 g sorbic acid, 20 g of pluronic F-127 and sufficient purified water to make 100 mL.

PACKAGING

Package in tight, light-resistant containers.

LABELING

For external use only. Keep out of reach of children.

STABILITY

No specific stability studies have been reported on this product.

DISCUSSION

Piroxicam is a nonsteroidal anti-inflammatory agent that is structurally unrelated to others in the same therapeutic class. It is only sparingly soluble in water and slightly soluble in alcohol and has a pKₐ of 5.1 in aqueous solution. It provides anti-inflammatory, analgesic and antipyretic activity and can cause gastrointestinal mucosal damage when given orally. Topical administration may minimize the incidence of these untoward effects. Lecithin varies somewhat depending upon its origin. Its color may range from a light yellow to brown, depending upon its source, crop variants and whether it has been bleached. It is generally odorless but may have a nut-like odor and a bland taste. It is partially soluble in water but will hydrate to form emulsions. It is used as an emulsifying and solubilizing agent.

Isopropyl palmitate is a colorless, mobile liquid with a very slight odor. It is soluble in acetone, castor oil, cottonseed oil, alcohol and mineral oil. It is insoluble in water, glycerin and propylene glycol. It is used as an oleaginous vehicle.

Pluronic F-127 is generally available in powdered form. It is either odorless or it may have a mild odor. It melts at about 56°C and is freely soluble in water, alcohol and isopropyl alcohol.

Sorbic acid (C₆H₈O₂, MW 112.13) is used as an antimicrobial preservative. It is a tasteless, white to yellow-white crystalline powder with a faint, characteristic odor. It melts at 134.5°C and is soluble 1 g in 400 mL of water at 30°C, 8 mL of ethanol, 10 mL of 95% ethanol, 320 mL of glycerin and 19 mL of propylene glycol. It is sensitive to oxidation, especially in light, and oxidation occurs more rapidly in aqueous solution. It may be stabilized by phenolic antioxidants, such as about 0.02% propyl gallate. It is incompatible with bases, oxidizing agents and reducing agents. It may lose some of its antimicrobial activity in the presence of nonionic surfactants and plastics. Sorbic acid is widely used as an antimicrobial preservative in oral and topical pharmaceutical formulations.

Purified water is water that is obtained by distillation, ion exchange, reverse osmosis or some other suitable process. Water has a specific gravity of 0.9971 at room temperature, a melting point at 0°C and a boiling point at 100°C. It is miscible with most polar solvents and is chemically stable in all physical states (ice, liquid and steam).

When counseling the patient concerning this product, it is advisable to explain its temperature-dependent viscosity. As the preparation is rubbed onto the skin and warms up, it may become slightly more viscous and resistant to rubbing.

References

A decade ago, Pluronic lecithin organogel (PLO), which has become one of the most versatile and effective vehicles in the history of compounding pharmacy, was developed by compounding pharmacist Marty Jones. His colleague Lawson Kloesel suggested adding Pluronic F-127 gel to stabilize the original formula. In this interview, Jones describes the process of creating this exceptional base for transdermal preparations and explains how and why it is effective. Several transdermal formulations that reflect the diversity of compounds made effective by the use of PLO are also provided.

Q: Of what does PLO consist?
MJ: PLO is an emulsion that has the appearance and feel of a gel. It consists of Pluronic F-127 20% to 30% (the aqueous phase of the formula) and a lipid phase of equal parts of lecithin and either isopropyl palmitate or isopropyl myristate (about 20% by weight or 22% by volume). Pluronic F-127 20% or 30% (a thermoreversible gel that must be refrigerated to ensure fluidity) and the combination of lecithin and isopropyl palmitate or isopropyl myristate (a solution) are made separately or can be purchased ready-made and are then usually combined with the active drug and a solvent by shear force (syringe to syringe for small volumes, electronic mortar and pestle, ointment mill). Shear force, which produces a micelle (bilayer, liposome) (Figure 1) that is small and uniform in size, must be used in the preparation of PLO. We know that when a PLO is prepared in a beaker or with a mortar and pestle, it just doesn’t work as well clinically as when shear force is used to prepare it. PLO must be made by a compounding pharmacist and is obtained by prescription for the individual patient. It is not available in different strengths. The use of medications in PLO to treat human patients runs the whole gamut.

Q: How was PLO developed?
MJ: In 1991, I attended a seminar at Professional Compounding Centers of America (PCCA), and David Sparks, the president and CEO of PCCA, commented to me that the development of a transdermal delivery system for use by compounding pharmacists would be tremendously valuable. About that time, I decided to subscribe to the American Pharmaceutical Association’s Journal of Pharmaceutical Sciences. In an article in the first issue that I received, reference was made to using Franz cells to test the transdermal delivery of six or eight different drugs, each of which had been combined with lecithin organogel. The researchers reported that the lecithin organogel interacted with the stratum corneum of the skin (Figure 2) and disrupted its lipid layers so that the drugs easily permeated that layer of skin. They concluded that the organogel might offer a novel and effective form of transdermal delivery. I was intrigued by that. I tried to obtain some lecithin, but at the time I couldn’t find any, so I used the contents of lecithin capsules. I then began to combine isopropyl palmitate with the lecithin in various proportions. I finally developed a spontaneous gel that consisted of about 20% lecithin in addition to isopropyl palmitate, and water that was easy to formulate and had the right physical characteristics. At the next PCCA seminar, I was asked to make a presentation on the subject, and the level of interest was enormous. The use of PLO has now grown immensely from its meager beginnings in the early 1990s, and new uses are constantly being identified. Drugs that I had never thought would work when combined with the gel (those that have large molecules and are water soluble, like insulin) are noted in anecdotal reports to be effective in PLO. It’s more versatile than I ever imagined a transdermal delivery system could be. Even combination medications such as the anti-nauseant ABHR (lorazepam [Ativan], diphenhydramine hydrochloride [Benadryl], haloperidol [Haldol], and metoclopramide hydrochloride [Reglan]), to which dexamethasone may be added, work really well in PLO.

Q: What is the mechanism of action of PLO?
MJ: The barrier to transdermal delivery is the stratum corneum. PLO disrupts the lipid layers of the stratum corneum without damaging them, as do harsher agents like dimethyl sulfoxide (DMSO), which dissolves the lipid layers. PLO allows the medication to slip through the stratum corneum...
into the systemic circulation via the dermal-epidermal blood flow so that it is more likely to be absorbed. We have found that administering a drug transdermally in PLO at the comparable oral or rectal dose is usually an effective initial dose. For example, prochlorperazine is usually prescribed at 5 to 10 mg per oral dose or up to 25 mg per suppository. We started the usual dose of prochlorperazine in PLO at 25- to 50-mg doses, and that seemed to work well. We found the same effect when we administered promethazine; a 25- to 50-mg topical dose is comparable to the usual oral or rectal dose. You start PLO dosing empirically and adjust the dose according to the needs of the individual patient.

Q: How did you improve the first formulation of PLO?

MJ: Lawson Kloesel, who is one of my colleagues at PCCA and is currently chairman of the board of PCCA, was also interested in this gel; and we began to work together on a way to improve the formulation. At that point, it was a nice-looking preparation; but it was a little unstable: the gel would separate a bit after it had been made. Lawson and I began to look for ways of improving the preliminary attempts at creating PLO, and he found another article in the *Journal of Pharmaceutical Sciences* about Pluronic F-127 gel. He began to work with Pluronic gel at room temperature, and over the next few months he tried everything that he could to get it into solution. At that time, it was January 1992, and it was rather cold in Houston. Lawson was working late in the lab, and when he left to go home, he packed his latest experiment with the gel into his briefcase, which he left for several hours in his car outdoors. When he opened his briefcase, the Pluronic gel, which was part of the experiment, was going into solution. Pure serendipity led us to discover that aspect of the gel, which we also found to be thermoreversible. When we combined the Pluronic gel with the lecithin and the isopropyl palmitate, we had a much more stable preparation and one that we could better work with.

Q: How was PLO evaluated clinically?

MJ: We began to collaborate with a few local physicians and their patients in the classic triad. When we were consulted by prescribers to see which analgesic formulations we’d suggest for a patient with knee pain, for example, we’d mention a new transdermal delivery system that might be effective. Most physicians were willing to prescribe it. At first, we used the gel in combination with nonsteroidal anti-inflammatory drugs such as ketoprofen to treat joint and arthritic pain. Then I had an HIV-demented hospice patient who had been treated with oral haloperidol but had become very difficult to manage. He had begun to resist treatment and to bite the staff who provided his care. This patient’s physician had prescribed an injection of haloperidol, but the staff was afraid to administer it. That physician had been prescribing my formulation of ketoprofen in PLO and asked whether I thought that haloperidol in PLO would also be effective. I said that we could certainly try, and we decided to initiate treatment with 5 mg of haloperidol per dose. The dose was prepared (5 mg haloperidol in 0.1 mL PLO) and was dispensed in 1-mL syringes with the instructions to apply 0.1 mL of the preparation 3 times daily to the patient’s back. Initially, three people had to restrain the patient to apply the gel.

During the next week, there was a mix-up in the transcription of the orders, and the medication nurse was applying 1 mL of the gel to the patient’s back 3 times daily. He was thus receiving 50 mg of haloperidol 3 times daily, and the classic signs of overdose developed: his speech became slurred, and he chewed on his tongue. We interrupted therapy with the haloperidol gel until the patient’s blood serum level of the drug had decreased, and we then resumed therapy at a dosage of 10 mg 3 times daily. That protocol was remarkably effective. The patient, instead of fighting and being belligerent, became calm and collected and was able to communicate better with his family until he died. That was our first case in which a drug that was effective by mouth and by injection also worked when applied topically in PLO. We presented those results at the next PCCA seminar, and pharmacists in the audience really began to “think outside the box.” When they had patients with problems or diseases that were refractory to treatment or when physicians were asking for help in determining an appropriate dosage form, they began to consider PLO as an effective vehicle.

Q: What was the next step in defining the uses of PLO?

MJ: Next I suggested prochlorperazine (a drug that is fairly specific for opioid-related nausea) in PLO for use in hospice patients. It’s hard to get a patient who is vomiting to swallow a tablet or capsule. In many of those patients, a suppository may be difficult or inappropriate to administer, and invasive therapy is not an option. The topical administration of prochlorperazine, however, produced great results. It was effective and easy to administer and could be applied almost anywhere: to the inner wrist, on the neck, on the upper torso. It worked so well that the hospice nurses asked that standing orders be left for its administration as needed by patients.
When we first began to prepare it, the compound contained 25 to 50 mg of prochlorperazine per dose for application several times daily. Then a medication nurse who had used the preparation to treat several patients during her shift complained of dizziness. We found that she had been exposed to the drug because she hadn’t worn a glove when she applied the gel, so we had to specify that precaution in the instructions for use. The caregiver must always use a glove when he or she applies the gel, and the patient should not touch the treated area or get the medication in his or her eyes or mouth. The treated area can be covered with a patch to prevent contact with clothing, and the patient should be aware that for several hours after application, the gel can be transferred to others with whom he or she has close physical contact. PLO washes off readily with water, so the area must not be washed until several hours after the dose has dried.

Q: Is PLO an effective vehicle for administering medications to pediatric patients?

MJ: Many clinical reports describe the effectiveness of promethazine in PLO for the treatment of nausea in children. Trying to administer oral syrup or a suppository may traumatize a child who is already distraught because of nausea, but rubbing a little promethazine in PLO into the patient’s skin can resolve the problem safely and much more pleasantly. PLO is also a very effective vehicle for administering secretin, which is usually given intravenously, to autistic children. Intravenous administration of a drug is very traumatic for children with autism and for their parents and the nursing staff. Secretin is unstable in water, so we made an anhydrous PLO and were able to provide the drug in an effective transdermal dose. Thousands of such doses have been administered to autistic children safely and with great benefit.

Q: Are any drugs not appropriate for use in PLO?

MJ: The use of antibiotics in PLO has not been well documented clinically in humans. We do have anecdotal reports in veterinary practice of the transdermal administration of antibiotics to the pinna of the ear in cats or dogs. Low-molecular-weight and lipid-soluble drugs such as hormones should be combined with a cosmetic hormone replacement therapy base instead of PLO. Other transdermally administered drugs that have a higher molecular weight and are more water soluble require a PLO-type vehicle. We also found that lidocaine, guaifenesin, and amitriptyline may break down PLO and cause it to be thin.

Q: How should preparations containing PLO be stored?

MJ: Most preparations that contain PLO should be stored at room temperature. If the active drug is not stable at room temperature, the gel must be refrigerated; and that can present problems because PLO may separate under refrigeration. Those preparations can be remixed by means of shear force to ensure micelle formation.

Q: Do caveats apply to the compounding of PLO?

MJ: For the past 10 years, PLO has been very effective in the marketplace. It is so versatile that we often wonder why we are surprised when a new and unlikely application of the gel works. It is a very successful preparation, but with success comes competition. Some pharmacists are making PLO improperly, but it’s essential to compound it correctly to get the best results.

Q: What is the future of PLO as a transdermal vehicle?

MJ: I’m amazed at the number of drugs used successfully in PLO over the past 10 years. Its future applications are as many as the opportunities to experiment with and clinically assess the efficacy of drugs in that vehicle. I’m pleased to have been part of the development of a transdermal base that is so effective, and it’s very rewarding clinically, professionally, and personally to help patients whose needs might otherwise have been unanswered.

For additional information about PLO, contact Marty Jones, BSPharm, FACA, FIACP, Professional Compounding Centers of America, 9901 South Wilcrest Drive, Houston, TX 77099. E-mail:mjones@pccarx.com.
# Sample Transdermal Compounds Using PLO

## Ketoprofen 10% in PLO

**For 100 mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>10 g</td>
</tr>
<tr>
<td>Alcohol or ethoxy diglycol</td>
<td>10 mL</td>
</tr>
<tr>
<td>Base, lecithin isopropyl palmitate</td>
<td>22 mL</td>
</tr>
<tr>
<td>solution(a) or lecithin isopropyl</td>
<td></td>
</tr>
<tr>
<td>myristate solution(b)</td>
<td></td>
</tr>
<tr>
<td>Base, Pluronic F-127 gel 20%(c)</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

**Use:** The treatment of joint and arthritic pain

Dissolve the ketoprofen in the ethyl alcohol or ethoxy diglycol. Add that phase to the lecithin isopropyl palmitate solution or the lecithin isopropyl myristate solution. Stir well. Add sufficient Pluronic F-127 gel 20% to a volume of 100 mL. Use an electronic mortar and pestle or (preferably) an ointment mill to mix the final product by means of shear force to encourage micelle formation. Store the mixture at room temperature.

## ABHR in PLO

**For 60 mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.06 g</td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>0.75 g</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.12 g</td>
</tr>
<tr>
<td>Metoclopramide hydrochloride</td>
<td>1.2 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>1 mL</td>
</tr>
<tr>
<td>Ethoxy diglycol</td>
<td>10 mL</td>
</tr>
</tbody>
</table>

| Base, lecithin isopropyl palmitate     | 14 mL    |
| solution\(a\) or lecithin isopropyl    |          |
| myristate solution\(b\)                |          |
| Base, Pluronic F-127 gel 20%\(c\)      | 60 mL    |

**Use:** The treatment of nausea

Dissolve the diphenhydramine hydrochloride and metoclopramide hydrochloride in the purified water. Dissolve the lorazepam and haloperidol in the ethoxy diglycol. Mix the two phases together. Add the resultant mixture to the lecithin isopropyl palmitate solution or the lecithin isopropyl myristate solution. Stir well. Add sufficient Pluronic F-127 gel 20% to a volume of 60 mL. Use an electronic mortar and pestle or (preferably) an ointment mill to mix the final product by means of shear force to encourage micelle formation. Each milliliter of the preparation contains lorazepam 1 mg, gabapentin 6 mg, and clonidine 2 mg. Store the mixture at room temperature.

## Ketamine Hydrochloride 10%, Gabapentin 6%, Clonidine Hydrochloride 0.2% in PLO

**For 100 mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine hydrochloride</td>
<td>11.5 g</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>6 g</td>
</tr>
<tr>
<td>Clonidine hydrochloride</td>
<td>0.22 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>10 mL</td>
</tr>
</tbody>
</table>

| Base, lecithin isopropyl palmitate     | 22 mL    |
| solution\(a\) or lecithin isopropyl    |          |
| myristate solution\(b\)                |          |
| Base, Pluronic F-127 gel 20%\(c\)      | 100 mL   |

**Note:** 1.1 mg of clonidine hydrochloride = 1 mg clonidine; 1.15 mg ketamine hydrochloride = 1 mg ketamine

**Use:** The treatment of nerve-related pain

Dissolve the ketamine hydrochloride, gabapentin, and clonidine hydrochloride powders in the purified water. Mix well into the lecithin isopropyl palmitate solution or the lecithin isopropyl myristate solution. Add the Pluronic F-127 gel 20% to a volume of 100 mL. Use an electronic mortar and pestle or (preferably) an ointment mill to mix the final product by means of shear force to encourage micelle formation. Each milliliter of the preparation contains ketamine 100 mg, gabapentin 60 mg, and clonidine 2 mg. Store the mixture at room temperature.

## Methimazole 5 mg/0.1 mL in PLO (Veterinary Formulation)

**For 3 mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methimazole</td>
<td>0.15 g</td>
</tr>
</tbody>
</table>

| Base, lecithin isopropyl palmitate     | 0.66 mL  |
| solution\(a\) or lecithin isopropyl    |          |
| myristate solution\(b\)                |          |
| Base, Pluronic F-127 gel 20%\(c\)      | 3 mL     |

**Use:** The treatment of thyroid disorders

Place the methimazole into a 5-mL Luer-Lok syringe from which the plunger has been removed and on which a tip cap is in place. Add the lecithin isopropyl palmitate solution or the lecithin isopropyl myristate solution. Carefully replace the plunger, remove the tip cap, and allow the air to escape from the syringe. Determine the volume of Pluronic F-127 gel to measure into another 5-mL syringe and attach a Luer-Lok or a Luer-Lok adapter. Connect the two syringes and mix the contents back and forth by means of shear force to ensure that a uniform micelle mixture is formed. Store the mixture at room temperature.

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\(a\)Formula for lecithin isopropyl palmitate solution in *IJPC* 2002;6:293.

\(b\)Formula for lecithin isopropyl myristate solution: substitute isopropyl myristate for isopropyl palmitate in the formulation for lecithin isopropyl palmitate solution cited in \(a\) above.

\(c\)Formula for Pluronic F-127 gel 20% in *IJPC* 2002;6:293.

PLO = Pluronic lecithin organogel
will result in increased viscosity up to a point where the sodium alginate is salted out, occurring at about 4% with sodium chloride. Tragacanth gum has been used to prepare gels that are most stable at pH 4 to 8. These gels must be preserved with either 0.1% benzoic acid or sodium benzoate or a combination of 0.17% methylparaben and 0.03% propylparaben. These gels may be sterilized by autoclaving. Since powdered tragacanth gum tends to form lumps when added to water, aqueous dispersions are prepared by adding the powder to vigorously stirred water. Also, the use of ethanol, glycerin or propylene glycol to prewet the tragacanth is very effective. If other powders are to be incorporated into the gel, they can be premixed with the tragacanth in the dry state.

Liqua-Gel™ (Paddock) is a nongreasy, water-soluble, liquid lubricating gel that can be used to dissolve or suspend a variety of topically applied dermatological agents. It contains purified water, propylene glycol, glycerin, hydroxypropyl methylcellulose, and potassium sorbate. Sodium phosphate and boric acid are used to buffer the gel to a pH of about 5.0. Diazolidinyl urea, methylparaben and propylparaben are included as preservatives. Its viscosity is about 80,000 cps at 25°C; it is a clear, colorless, viscous gel with a faint, characteristic odor.

Quality Control

Quality control procedures include appearance, uniformity, weight/volume, viscosity, clarity, pH and smell.

Storage

Gels should be stored at refrigerated or room temperatures in tight containers. They should be labeled to be kept tightly closed.

Stability

Physical observations for gels include shrinkage, separation of liquid from the gel, discoloration and microbial contamination. Many gels will neither promote bacterial or mold growth nor prevent it. Consequently, they should either be autoclaved or contain preservatives. Gelling agents in the dry state are usually not a problem. Beyond-use dates for water-containing formulations are not later than 14 days, when stored at cold temperatures, for products prepared from ingredients in solid form. This is extended if there is supporting valid scientific stability information.
**Introduction**

An abundance of analgesic and pain-killing medications is available for use in current medicine. However, the major challenge with many pain medications and the cause of undesirable side effects is that, to provide local pain relief, high quantities of the drug must first be systemically administered. While distributing to the target tissues to achieve the therapeutic effect, these drugs often accumulate in nontarget organs, which can result in minor unwanted side effects, such as nausea, vomiting, dizziness and fatigue or more serious complications such as gastrointestinal injury with nonsteroidal anti-inflammatory agents (NSAIDs) or nonselective prostaglandin synthetase-cyclooxygenase (COX) inhibitors. In many instances, pain and inflammation are not systemic problems and are usually localized to one part of the body, such as the knee. Theoretically, there is no need for systemic administration of a drug that is meant to treat a localized malady. Therefore, a major challenge faced by healthcare providers is finding a suitable route of administration and a vehicle that can administer localized pain relief using drugs proven to be effective, while minimizing systemic side effects.

**Mechanism of Pain**

Pain is a condition that is frequently secondary to an underlying disease state, such as arthritis, or a result of an injury.

However, when a patient experiences pain, a primary responsibility of a healthcare provider is to alleviate that pain. To understand how to treat pain, one must understand the mechanisms by which pain manifests. The major mechanisms of pain production are as follows:

- **Prostaglandin release**–Prostaglandins are released under stress conditions such as heat, trauma, inflammation, etc. Prostaglandins exhibit a chemical stimulus effect on nociceptors that results in an increased perception of pain. Nociceptors, otherwise known as pain receptors, are most prevalent in the skin and provide a sensory neuronal pathway to the brain, which allows the sensation of pain.

- **Substance P**–Substance P is a stimulatory neuropeptide that prolongs the excitation of nociceptors and prolongs the duration of pain.

**Drugs Used to Treat Pain**

Drugs available for the management of pain are varied and wide reaching and include opioids, narcotics, neurolytics, local anesthetics and NSAIDs, as well as many more. For purposes of local analgesic properties, this article focuses primarily on local anesthetics and NSAIDs.

Local anesthetics, such as lidocaine, can also be used for temporary alleviation of pain and are a common additive in analgesic topicals. NSAIDs act primarily to decrease the formation of prostaglandins, thereby decreasing pain. NSAIDs proven effective for topical use are piroxicam (which was available in a commercially manufactured product), ketoprofen, diclofenac, aspirin and ibuprofen.

**Vehicle for Delivering Topical Analgesia: Pluronic Lecithin Organogel**

A common mechanism for providing localized drug delivery for pain relief is through the use of transdermal dosage forms such as ointments, creams, gels and lotions. Local drug delivery through the skin involves penetration through the skin layers. The epidermis, or topmost skin layer, provides the strongest protection against drug absorption and is composed of five different sublayers:

1. Stratum corneum,
2. Stratum lucidum,
3. Stratum granulosum,
4. Stratum spinosum and
5. Stratum basale.

Of these five layers, the stratum corneum is the most impermeable and can be compared structurally to a brick wall. Just as a brick wall consists of bricks and mortar, the stratum corneum consists of flattened cornified cells similar to bricks, which are embedded in a lipid intercellular matrix similar to...
hydrogen-bonding lattice.

Specifically, the properties of transdermal vehicles must be balanced so that they can deliver hydrophilic as well as hydrophobic drugs through the epidermal layer. A number of hydrocarbon-based vehicles, e.g., petrolatum, that contain very small amounts of water have not been able to successfully deliver most drugs through the epidermal layer.

In recent years, topical hydrogels consisting of about 50% w/w water, Pluronic and lecithin have become very popular in the topical delivery of drugs. A number of studies have shown that Pluronic lecithin organogels (PLOs) have the unique capacity to deliver drugs across the epidermal barrier and deliver particular medications such as NSAIDs and local anesthetics to a specific site.5,6

PLO Base
The PLO base is composed of three main ingredients: Pluronic gel, lecithin and isopropyl palmitate. In general, a gel is a two-phase colloidal system containing a solid and a liquid phase (water in pharmaceutical gels). Gels formed with poloxamers (Pluronic) are liquid (sol) at cold temperatures and undergo a phase change (gel) when the temperature is elevated. (In Figure 1, the shaded portion represents the gel area.) For optimal efficacy, 20% w/w of Pluronic F127 retains the gel structure from 20 to 70°C. This characteristic makes it useful in pharmaceutical compounding because it can be drawn into a syringe for accurate dose measurement when it is cold. The degree of viscosity of the Pluronic gel is dependent on the ratio of Pluronic to water; the higher the Pluronic concentration, the higher the viscosity. Pluronic is a reverse thermal gel, and its viscosity increases with higher temperatures, such as from the refrigerator to room temperature to application to the skin, which allows enhanced permeation of the gel and the active drug through the stratum corneum.11 It is evident that the lecithin component of PLO has the ability to act as an amphoteric surfactant and enables many drugs to penetrate into the dermal layer. The major advantages of PLO gels over other topical gels are:

- Compatibility with diverse systems owing to their nonionic nature,
- Low toxicity,
- No need of any neutralizer (compared to Carbopol gels) during preparation and
- Surfactant properties that enhance penetration.

Isopropyl Palmitate
Isopropyl palmitate acts as a solubilizing agent for lecithin and also as a nonoleaginous emollient with good spreading characteristics. It is a clear, colorless to pale yellow-colored, practically odorless viscous liquid that solidifies at less than 16°C. It should be stored in well-closed and light-resistant containers. The inclusion of isopropyl palmitate imparts the name organo to this product.

Enhancement of Bioavailability
In the past, topicals have had relatively poor local tissue availability. With the advent of PLO, the problem of bioavailability has been somewhat resolved. PLO provides an adequate vehicle that permeates the stratum corneum, thereby increasing the amount of available drug. Because lecithin is a
Some earlier studies that used lecithin as a transport medium and practitioners. When a water-soluble drug is added to a hydrophobic substance, with the aid of a surfactant, both the drug and the hydrophobic medium can pass through the epidermis. Some earlier studies that used lecithin as a transport medium were with scopolamine. Figure 2 demonstrates the in vitro transport of scopolamine through human skin; the upper shaded area on the graph represents soybean lecithin-mediated transport of scopolamine in two different experiments; and the lower shaded area represents a control buffered medium in corresponding experiments. This figure indicates that a soybean lecithin extract has a greater ability to pass through the human skin. Experiments such as the one described here have led to efforts to transport other types of medications using PLOs. With the aid of PLO, low-molecular-weight hydrophilic drugs can now be successfully delivered, thereby increasing the range of therapeutic options available to patients and practitioners.

**Clinical Studies With Topical NSAIDs**

Reports on various forms of localized topical analgesia have appeared in the literature since the 1960s, with the main applications being for burn therapy, herpes lesions, dentistry and oral trauma medicine and for various local anesthetics. In 1982, the results of the first controlled clinical trial (n = 60) using an eutectic mixture of two local anesthetics (EMLA, prilocaine and lidocaine) were published and demonstrated a highly statistically significant difference in the experience of pain due to venous cannulation in favor of EMLA compared with placebo. In 1982, the results of the first controlled clinical trial (n = 60) using an eutectic mixture of two local anesthetics (EMLA, prilocaine and lidocaine) were published and demonstrated a highly statistically significant difference in the experience of pain due to venous cannulation in favor of EMLA compared with placebo.
recent years, many review articles evaluating the efficacy and toxicity of topical versus oral NSAIDs have been published.17-21

Studies have also been published comparing the efficacy of various topical gel formulations,22-30 patches31 and creams.32 Incidentally, topical gels of COX-2 inhibitors have been shown to be less effective than the various nonselective NSAID topicals in providing pain relief.33

### Pharmacokinetics of NSAIDs Following Topical Application

Skin permeability and local-tissue concentrations of salicylic acid, diethylamine salicylate, indomethacin, naproxen, diclofenac and piroxicam from topically applied aqueous solutions were found to be dependent on the drug’s lipophilicity.14

The tissue distribution of ketoprofen following topical gel administration was evaluated in six patients15 and found to be 4.7 µg/g in the intra-articular adipose tissue, 2.35 µg/g in the capsular sample and 1.4 µg/g in the synovial fluid (plasma concentrations, evaluated from plasma drawn at the same time, were 100 times lower than the concentration in the synovial fluid). The pharmacokinetics of ketoprofen after repeated percutaneous administration of a 2.5% ketoprofen gel (corresponding to a 375-mg daily dose spread over a 750-cm² area) was evaluated in 10 healthy subjects.16 The peak plasma concentration was 144 ± 91 ng/mL after the first administration, with apparent absorption and elimination half-lives of 3.2 ± 2.4 hours and 27.7 ± 18.0 hours, respectively. The total quantities of ketoprofen eliminated in the urine represented about 2.6% of the first dose applied. At the end of the 10-day chronic administration period, the apparent half-life of unchanged ketoprofen was 17.1 ± 9.1 hours; there was no accumulation and no sign of local intolerance.

Figure 3 compares the areas under the dialysate concentrations versus time curves (detector response) up to 5 hours after administration of 100-mg ketoprofen (intramuscular injection versus topical application) with those of 800 mg ibuprofen (oral administration versus topical application). Ibuprofen concentrations in muscle were highly variable and considered effective in only half of the subjects. In contrast to ketoprofen, concentrations of subcutaneous ibuprofen after topical administration clearly exceeded those after oral dosing; ibuprofen from a gel formulation reliably reached high concentrations in subcutaneous tissue, but not muscle tissue, after topical administration.37

### Side Effects

Although the ketoprofen in PLO does not totally eliminate the risk of some side effects due to systemic absorption, the probability of experiencing such side effects is enormously reduced. The major side effects associated with the topicals are rash and irritation at the site of application. The eye irritation test for 10% aqueous solution (pH 7.2) of Pluronic F127 was zero, and the dermal LD50 was >5g/kg, with insignificant skin irritation.7

### Instructions for Use

NSAIDs in PLO should be applied topically to affected areas. Before applying, the patient should put on protective gloves, if available, and thoroughly clean the application site. After application, patients may experience a normal warming or cooling sensation; the sensation does not indicate an allergic reaction. If the patient has a sensitivity to egg whites, he or she might have an allergic reaction due to the lecithin content of the gel base. As a precaution, patients need to be aware that the preparation contains an NSAID and should not be used if they are hypersensitive to the active drug or any other NSAID. When storing the PLO, patients should keep the preparation out of the reach of children, protected from air and light and at a controlled room temperature to prevent degradation.

### Conclusion

With the advent of PLO, physicians, dentists and other healthcare providers now have the opportunity to treat their patients’ pain with a topical vehicle base for analgesic drugs that would otherwise have to be taken by injection or by mouth. Advantages of this dosage form range from a significant reduction of severe side effects to increased patient compliance. Also, PLOs have the advantage of being able to act at a specific and localized area, increasing the potential analgesic effects at the painful site. However, PLO creams are not a cure-all. Like all dosage forms, they can have side effects, such as local irritation at the site of application; and the spectrum of drugs available for use is obviously limited by the drug’s physicochemical properties. Despite these factors, overall, the PLO topical dosage form appears to be an effective alternative method for delivering pain relief that both the patient and the practitioner can value.

### References


Address correspondence to: Sudip K. Das, PhD, MPPharm, College of Pharmacy, Idaho State University, 970 South 5th Avenue, Pocatello, Idaho 83209-8334.

E-mail: das@pharmacy.isu.edu
Since propylene glycol is hygroscopic, it should be stored in well-closed containers and protected from light. It should be stored in well-closed containers and protected from light.

Propylene glycol (C₃H₈O₂) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste, somewhat resembling glycerin. It has a specific gravity of 1.038 g/mL and is miscible with acetone, chloroform, 95% ethanol, glycerin and water. Since propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light.

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatides, consisting chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidyserine and phosphatidylinositol, in combination with triglycerides, fatty acids and carbohydrates. The composition and physical properties vary depending upon the source of the lecithin and the degree of purification. Lecithin is used as an emollient, emulsifying agent and solubilizing agent in topicals, inhalation aerosols, parenterals and oral suspensions. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending upon whether it is bleached or unbleached. It is practically insoluble in water, polar solvents and cold vegetable and animal oils; when mixed with water, though, it hydrates to form emulsions. It is soluble in aliphatic and aromatic hydrocarbons, mineral oil and fatty acids. It will decompose at extremes of pH, is hygroscopic and is subject to microbial degradation. It should be stored in well-closed containers and protected from light.

Isopropyl palmitate (C₁₉H₃₈O₂, MW 298.51) is a colorless, mobile liquid with a very slight odor that is used as an emollient, oleaginous vehicle and a solvent; it has good spreading characteristics. It is soluble in acetone, castor oil, cottonseed oil, alcohol and mineral oil. It is insoluble in water, glycerin and propylene glycol. It should be stored in well-closed containers and protected from light.

Poloxamer 407 (Pluronic F-127) is generally available in powdered form. It is either odorless or may have a very mild odor. It melts at about 56°C and is freely soluble in water, alcohol and isopropyl alcohol. The pH of a 2.5% w/v aqueous solution is in the range of 6.0 to 7.4. The poloxamers are stable and aqueous solutions are stable in the presence of acids, alkalis and metal ions; but the aqueous solutions do support mold growth.

**References**

Preparation and Evaluation of Sustained Drug Release from Pluronic Polyol Rectal Suppositories

Abstract

Suppository dosage forms offer several advantages in drug delivery and can be compounded in a pharmacy setting for the needs of the individual patient. In this study, we have examined the use of Pluronic polyols in the development of sustained-release rectal suppository formulations. Solid and liquid Pluronic polyols (Pluronic L61, F68, L101, and F108) were combined in a weight ratio ranging from 80:20 (solid to liquid) to 70:30 to prepare the bases. The release behavior of a model drug, riboflavin, from the suppositories was evaluated by means of the United States Pharmacopeia Basket Dissolution Method. When compared with the control Polybase suppository, which released 50% of the drug (t50) in about 7.23 minutes, Pluronic F68/L61 suppositories at an 80:20 weight ratio exhibited a t50 of 86.5 minutes (1.44 hours). Riboflavin release from suppositories made with Pluronic F108/L101 was even further delayed. The t50 of riboflavin from Pluronic F108/L101 suppositories at an 80:20 weight ratio, for instance, was 274.4 minutes (4.6 hours). The results of this study show that by choosing specific combinations of Pluronic polyols and weight ratios, compounding pharmacists can prepare sustained-release suppository formulations that can deliver drugs within minutes to hours. This flexibility of compounding sustained-release suppositories is beneficial, especially for the management of chronic pain in cancer patients.

Introduction

Suppositories are semisolid dosage forms that are used for drug administration into the rectum, vagina, or urethra.1 Rectal suppositories are used for local or systemic therapy. The indications for suppository formulations include localized conditions such as constipation, hemorrhoids, itching, and infections. A suppository delivery system is appropriate for drugs such as steroid hormones that undergo high first-pass metabolism on oral administration. The hydrogel formulation, unfortunately, requires sophisticated preparation skills and machinery and would not be practical for many compounding pharmacies.6

As a result of the need to formulate sustained-release suppository formulations at the pharmacy practice site, we have investigated the use of Pluronic polyol blends as water-soluble suppository bases. As shown in Figure 1, Pluronic polyols are triblock copolymers of poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) (PEO/PPO/PEO) manufactured by BASF Corporation in Parsippany, New Jersey. More than 35 different types of Pluronic polyols with varying chain lengths of PEO and PPO segments are available.7 They are used in a number of pharmaceutical and cosmetic applications as nonionic surfactants.8 Pluronic F127 (MW 12,500 Da), a triblock copolymer containing 96 residues of ethylene oxide and 69 residues of propylene oxide, is used to make Pluronic/lecithin gel (Organogel). A 20% to 25% (w/w) aqueous solution of Pluronic F127 changes from a liquid to a gel when the temperature is increased to more than 21°C.9

Four different types of Pluronic polyols (Pluronic L61, F68, L101, and F108) were selected for the preparation of the suppository base. PF68 (melting point, 52°C) and PF108 (melting point, 57°C) are higher-molecular-weight solids with longer PEO chains. Riboflavin (vitamin B2), a model drug, was incorporated in the Pluronic base, and the in vitro release was examined by means of the United States Pharmacopeia (USP) Rotating Basket Dissolution Method.10

Materials and Methods

Materials
Riboflavin (vitamin B2, MW 376.4 Da) was purchased from
Sigma Chemical Company in St. Louis, Missouri. Pluronic L61, F68, L101, and F108 (Table 1) were obtained from BASF Corporation. Pluronic F68 and F108 were of National Formulary (NF) grade. The liquid pluronics, which are not available as NF grade, were of the purity supplied by the manufacturer. Deionized distilled water (NanoPure II, Barnsted-Thermolyne, Dubuque, Iowa) was used to prepare all aqueous solutions. All other chemicals and reagents were of analytical grade and were used as received.

Preparation of Riboflavin-Containing Pluronic Polyol Suppositories

Riboflavin-containing Pluronic polyol suppositories were prepared by mixing a known amount of the drug with Pluronic F68 and L61 or Pluronic F108 and L101. The Pluronic blends were mixed in weight ratios ranging from 80:20 (solid to liquid) to 70:30. Increasing the quantity of Pluronic L61 or L101 above 30% (w/w) resulted in suppositories that were too fragile and were difficult to remove in one piece from the mold. Measured quantities of PF68/PL61 or PF108/L101 were added to a glass beaker, and the mixture was allowed to warm up to 60°C on a hot plate while being stirred continuously with a glass rod. When the solid Pluronic polyols (PF68 or PF108) had completely melted and were uniformly mixed, the molten mixture was removed from the hot plate and riboflavin powder was added via continuous mixing to ensure uniform drug distribution. The amount of riboflavin added was based on the dose of 25 mg per each 2.0-g rectal suppository.

Table 1. Properties of Poly(Ethylene Oxide)/Poly(Propylene Oxide)/Poly(Ethylene Oxide) Triblock Copolymers (Pluronics) Used for the Preparation of Suppository Bases.7

<table>
<thead>
<tr>
<th>Copolymer</th>
<th>Abbreviation</th>
<th>Physical State at Room Temperature</th>
<th>Average Molecular Weight</th>
<th>Melting Point (°C)</th>
<th>No. EO/PO/EO Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pluronic L61</td>
<td>PL61</td>
<td>Liquid</td>
<td>2000</td>
<td>–</td>
<td>3/30/3</td>
</tr>
<tr>
<td>Pluronic F68</td>
<td>PF68</td>
<td>Solid</td>
<td>8350</td>
<td>52</td>
<td>75/30/75</td>
</tr>
<tr>
<td>Pluronic L101</td>
<td>PL101</td>
<td>Liquid</td>
<td>3800</td>
<td>–</td>
<td>6/56/6</td>
</tr>
<tr>
<td>Pluronic F108</td>
<td>PF108</td>
<td>Solid</td>
<td>14,000</td>
<td>57</td>
<td>122/56/122</td>
</tr>
</tbody>
</table>

EO, ethylene oxide; PO, propylene oxide.

Table 2. Initial Riboflavin Release Rate and Time for 50% Release (t50) from Polybase (Control) and Pluronic Suppositories.

<table>
<thead>
<tr>
<th>Suppository Formulation</th>
<th>Initial Release Ratea (mg/min)</th>
<th>Time for 50% Releaseb (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polybase</td>
<td>0.300 ± 0.014c</td>
<td>7.23 ± 1.85</td>
</tr>
<tr>
<td>PF68/PL61 (80:20)</td>
<td>0.096 ± 0.001</td>
<td>86.49 ± 1.82</td>
</tr>
<tr>
<td>PF68/PL61 (75:25)</td>
<td>0.140 ± 0.002</td>
<td>58.73 ± 1.88</td>
</tr>
<tr>
<td>PF68/PL61 (70:30)</td>
<td>0.122 ± 0.011</td>
<td>63.23 ± 8.23</td>
</tr>
<tr>
<td>PF108/PL101 (80:20)</td>
<td>0.057 ± 0.003</td>
<td>274.4 ± 15.2</td>
</tr>
<tr>
<td>PF108/PL101 (75:25)</td>
<td>0.062 ± 0.002</td>
<td>241.9 ± 9.87</td>
</tr>
<tr>
<td>PF108/PL101 (70:30)</td>
<td>0.065 ± 0.003</td>
<td>243.5 ± 13.2</td>
</tr>
</tbody>
</table>

a. The initial riboflavin release rate was obtained by linear regression analysis of the first four data points of amount released as a function of time plot.
b. The time for 50% release was calculated from the equation of the straight line obtained by linear regression analysis of the log-log plot of percent release as a function of time.
c. Mean ± SD, (n = 4).

Sigma Chemical Company in St. Louis, Missouri. Pluronic L61, F68, L101, and F108 (Table 1) were obtained from BASF Corporation. Pluronic F68 and F108 were of National Formulary (NF) grade. The liquid pluronics, which are not available as NF grade, were of the purity supplied by the manufacturer. Deionized distilled water (NanoPure II, Barnsted-Thermolyne, Dubuque, Iowa) was used to prepare all aqueous solutions. All other chemicals and reagents were of analytical grade and were used as received.

Preparation of Riboflavin-Containing Pluronic Polyol Suppositories

Riboflavin-containing Pluronic polyol suppositories were prepared by mixing a known amount of the drug with Pluronic F68 and L61 or Pluronic F108 and L101. The Pluronic blends were mixed in weight ratios ranging from 80:20 (solid to liquid) to 70:30. Increasing the quantity of Pluronic L61 or L101 above 30% (w/w) resulted in suppositories that were too fragile and were difficult to remove in one piece from the mold. Measured quantities of PF68/PL61 or PF108/PL101 were added to a glass beaker, and the mixture was allowed to warm up to 60°C on a hot plate while being stirred continuously with a glass rod. When the solid Pluronic polyols (PF68 or PF108) had completely melted and were uniformly mixed, the molten mixture was removed from the hot plate and riboflavin powder was added via continuous mixing to ensure uniform drug distribution. The amount of riboflavin added was based on the dose of 25 mg per each 2.0-g rectal suppository.

The drug-containing liquid mixture was gently poured into an aluminum rectal suppository mold that had been kept in a refrigerator so that the suppositories would congeal. Prelubrication of the mold with mineral oil or another lubricant was unnecessary for the Pluronic suppositories. After about 30 minutes in the refrigerator (~ 4°C), the suppositories were removed from the mold and were individually packaged in aluminum foil. They were stored in the refrigerator. Polybase (Paddock Laboratories, Inc, Minneapolis, Minnesota), a water-soluble suppository base made with polyethylene glycol (MW 400 Da [liquid], 8000 Da [solid]) and polysorbate-80 (a nonionic surfactant), was used as a control.

In Vitro Release of Riboflavin

The in vitro release of riboflavin from Pluronic polyol rectal suppositories was determined according to the method described by Zia et al.11 by means of the USP Rotating Basket Dissolution Method (also referred to as Apparatus 1). A riboflavin-containing PF68/PL61 or PF108/PL101 suppository was placed in a basket of a VK-7000 automated dissolution apparatus (VanKel Industries, Inc, Edison, New Jersey). The baskets were rotated at 50 rpm in 400 mL of phosphate-buffered saline (PBS, pH 7.4) at 37°C. Periodically, 3 mL of the PBS solution was removed from the dissolution vessel and was replaced with fresh buffer to keep the volume constant. The released riboflavin was assayed by measuring the absorbance of solution at 445 nm with a UV/VIS spectrophotometer (Shimadzu, Columbia, Maryland). The cumulative amount of...
riboflavin released was calculated by means of a calibration curve. The percent riboflavin released was obtained by dividing the amount released by the total amount present (25 mg) and multiplying the ratio by 100.

**Statistical Analysis**

Statistical analysis of the results was performed with Excel (Microsoft, Redmond, Washington) software. Average values ± standard deviation from at least four independent experiments are reported.

**Results and Discussion**

Liquid (PL61 and PL101) and solid (PF68 and PF108) Pluronic polyols were mixed to prepare a water-soluble suppository base for sustained release of the drug, which was evenly dispersed in the suppository matrix. As shown in Figure 2, the suppositories made with Pluronic base were pharmaceutically elegant. A conventional suppository compounding apparatus was used to make these sustained-release rectal suppositories, which is a significant benefit. The method of fabrication was simple enough to be accomplished in any compounding pharmacy.

Figure 3 shows the release kinetics of riboflavin from Polybase (control) and Pluronic F68/L61 suppositories. Polybase suppositories released riboflavin very rapidly and had completely dissolved in the release medium in less than 1 hour. Initial release rates were calculated by linear regression analysis of the first four data points. The time for 50% release was calculated from the equation of the straight line obtained from regression analysis of the log-log plot of percent release versus time. The initial rate of riboflavin release and the time for 50% of the drug to be released (t50) from Polybase suppositories were 0.300 mg/min and 7.23 minutes, respectively (Table 2). In some instances (for example, when local action to treat hemorrhoids or constipation is necessary), rapid drug release is desired. For systemic therapy, however, such fast release of the drug could actually lead to significant premature loss by excretion. In addition, it is desirable to have sustained drug-release suppository formulations for use in long-term therapy such as pain management. The release of riboflavin from PF68/PL61 suppositories, on the other hand, was much slower than that from Polybase suppositories. For example, the release rate from PF68/PL61 suppositories with a weight ratio of 80:20 was 0.096 mg/min, and the t50 was about 86.5 minutes. PF68/PL61 (80:20) suppositories released about 90% of the drug in about 4.5 hours. Increasing the concentration of PF68 in the formulation to 30% (w/w) decreased the t50 to about 63.23 minutes. PF68/PL61 (70:30) suppositories released 90% of the drug in about 3.5 hours.

As shown in Figure 4, riboflavin release from PF108/PL101 suppositories was even further delayed than that observed with PF68/PL61 suppositories. It is expected that drug release from watersoluble polymers (such as Pluronic polyols) upon hydration occurs by dissolution of the polymer rather than by diffusion. As such, PF108 and PL101, which have a higher molecular weight than PF68 and PL61, have a lower dissolution rate in an aqueous medium. The higher molecular weight of PF108 and PL101 may contribute to the slow dissolution rate of those polymers. The release rate of riboflavin from PF108/PL101 (80:20) suppositories was 0.057 mg/min, and the t50 was 274.4 minutes (Table 2). Even after 10 hours, only about 73% of the drug had been released from PF108/PL101 (80:20) suppositories. Increasing the PL101 concentration to 30% (w/w) facilitated the release of riboflavin. The release rate and the t50 of PF108/PL101(70:30) suppositories were 0.065 mg/min and
243.5 minutes, respectively. After 8 hours, about 95% of the drug had been released from PF108/PL101(70:30) suppositories.

Conclusion

A sustained-release suppository formulation offers several advantages for drug delivery to chronically ill patients. We investigated the release of a model drug, riboflavin, from a Pluronic polyol water-soluble suppository base as a function of the type of Pluronic used and the weight ratio. The results of this study indicate that sustained-release rectal suppositories can be designed for the particular needs of the patient. Compounding pharmacists can prepare a suppository formulation that can release a drug for up to 8 hours. This type of formulation benefits patients requiring long-term therapeutic management, such as pain control in cancer patients.

Acknowledgement

We are grateful to BASF Corporation for supplying the various Pluronic polyols used in this study.

References


Figure 4. Percent Riboflavin Released from Polybase (Control) and Pluronic F108/L101 Rectal Suppositories in Phosphate-Buffered Saline (pH 7.4) at 37°C.
Subject Review

Transcutaneous Drug Delivery: A Practical Review

JEFFREY J. BERTI, M.D., AND JAMES J. LIPSKY, M.D.

- **Objective:** To describe the advantages, disadvantages, practical considerations, and future developments of transcutaneous drug delivery.
- **Material and Methods:** The physiochemical properties of the drug preparation that are factors in the effectiveness of transcutaneous transport are drug stability or volatility, use of a solvent carrier or vehicle, use of a penetration enhancer, and type of delivery device. Because a drug should remain on the skin without evaporating or becoming otherwise inactive, it is suspended in a vehicle—any gel, lotion, or paste used to apply the drug to the skin. Penetration enhancers include several compounds that are mixed into vehicles to alter the molecular environment of the epidermis and facilitate absorption. The delivery system itself occasionally proves to be the ultimate determinant of transdermal drug flow.

- **Results:** The advantages of transcutaneous drug delivery are avoidance of the gastrointestinal tract and hepatic first-pass biotransformation and metabolism, control of absorption, availability of multiple skin sites to avoid local irritation and toxicity, and improved patient compliance. The disadvantages include the potential for localized irritant and allergic cutaneous reactions, systemic toxicity, and difficulties associated with the time necessary for a drug to diffuse through the skin.
- **Conclusion:** Transdermal drug regimens are safe and effective. They provide clinicians the opportunity to offer more therapeutic options to their patients to optimize their care.


GI = gastrointestinal

The skin, the largest organ of the human body, has proved to be a complex tissue of metabolic, immunologic, and sensory capability. Most physicians agree, however, that the skin has evolved for the primary purpose of protection, including the maintenance of fluid and electrolyte balance in our harsh, dry environment by preventing transepidermal water loss, as well as protection from microbial invasion and physical, chemical, and ultraviolet radiation-induced injury. Despite these types of protection, scientists have known for at least 2 centuries that certain compounds have the ability to traverse the layers of the skin and obtain access to blood vessels and the general circulation. Modern medicine has responded with the development of methods to deliver drugs transcutaneously (through the skin) for therapeutic use as an alternative to traditional routes including oral, intravascular, intramuscular, subcutaneous, and sublingual. Transcutaneous drug delivery has many theoretic and practical advantages and disadvantages, and such issues are often a concern for both clinicians and patients. This review of this relatively novel method of drug delivery serves as a foundation to address these concerns and provides practical knowledge for clinicians to optimize patient care.

**STRUCTURE OF THE SKIN**

In order to understand how drugs permeate the skin, basic knowledge of the structure of the skin is needed. The skin is composed of the epidermis, dermis, and underlying subdermal tissue (Fig. 1). The epidermis and dermis are separated by a basement membrane, whereas the dermis remains continuous with the subcutaneous and adipose tissues. The epidermis is composed of five layers of cell types, beginning from the outside of the skin—stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Within the dermis lie varying numbers of hair follicles and sebaceous glands along with apocrine and eccrine sweat glands, all supported by a rich vascular network.1 Relative to transcutaneous drug absorption, the molecular environment of the epidermis, most notably the cornified layer of the stratum corneum, provides the rate-limiting step to drug penetration (Fig. 1).2

The structure of the stratum corneum has been compared to that of “bricks and mortar”; 10 to 15 layers of flattened cornified cells constitute the bricks, and a lipid-rich intercellular matrix constitutes the mortar.3 This densely packed cellular and lipid apparatus forms an effective barrier to
TRANSCUTANEOUS ABSORPTION
The generally accepted theory is that transcutaneous absorption occurs through the intercellular lipid mortar rather than through the cellular bricks. The factors that control the absorption of drugs across the skin are related to the classic principles of diffusion across semipermeable membranes that involve each component of the skin. The transcutaneous flow of compounds across the stratum corneum is directly proportional to the concentration gradient and therefore can be attributed to passive diffusion. Highly lipophilic compounds with low molecular weight demonstrate the greatest flow rate through the stratum corneum. Additionally, as the surface area exposed to a drug increases and as the thickness of the epidermis decreases, the rate of transdermal flux increases. For compounds used exclusively for the treatment of a skin condition, passive diffusion into the superficial epidermis may be sufficient. For a drug to be delivered to the general circulation, however, it must not only diffuse through the lipid matrix of the stratum corneum but also traverse the aqueous environment of the remaining underlying epidermal layers and dermis. Highly lipophilic drugs diffuse through the lipid mortar quickly but are slowed when they reach the aqueous layers of the epidermis. The opposite is true for polar hydrophilic compounds; the primary barrier is in fact the outer lipid layers of the stratum corneum. Therefore, the drug must maintain affinity for both lipid and aqueous environments for effective absorption. The oil:water partition coefficient of the drug—that is, its relative solubility in oil versus water—and the polarity of the drug must then be considered. Scientists must approach the development of transdermally delivered drugs with this concept in mind.

Several other physicochemical properties of the drug preparation are factors in the effectiveness of transcutaneous transport, including drug stability or volatility, use of a solvent carrier or vehicle, use of a penetration enhancer, and type of delivery device. A drug should remain on the skin without evaporating or becoming otherwise inactive due to spontaneous chemical breakdown. A simple method to accomplish this situation has been to suspend the drug in a vehicle—any gel, lotion, or paste used to apply the drug to the skin. Penetration enhancers include several compounds that are mixed into vehicles to alter the molecular environment of the epidermis, most often the lipid mortar of the stratum corneum, and facilitate drug absorption. Finally, the delivery system itself occasionally proves to be the ultimate determinant of transdermal drug flow. A simple patch-type delivery system is shown in Figure 2. The basic system consists of adhesive and a drug reservoir with or without a rate-controlling membrane, all covered by an occlusive backing. Drug-delivery devices have been designed to control the rate of drug diffusion into the skin; they are not used to apply the drug as an ointment or lotion. Each of these factors becomes interdependent in the determination of the final rate of transcutaneous drug delivery. The pharmacokinetics resulting from these interactions may prove to be complex; the methods and models involved are the subject of intense research beyond the scope of most clinicians.

TRANSCUTANEOUS DRUG DELIVERY
Advantages.—Clinically, the decision to use transdermal drug delivery is based on the relative advantages and disadvantages for the patient. Advantages include the following: avoidance of the gastrointestinal (GI) tract and hepatic first-
pass biotransformation and metabolism, control of absorption, availability of multiple skin sites to avoid local irritation and toxicity, and improved patient compliance.\textsuperscript{13} Therapeutic levels of a drug such as nitroglycerin can be achieved with much lower dosages and with tighter control in light of the fact that absorption occurs on a limited area of the skin rather than the drug being exposed to large areas of the GI tract and hepatic first-pass metabolism. Furthermore, the biochemical environment of the GI tract, including the acidic environment of the stomach, the influence of food, and the presence and influence of normal gut flora, can be avoided. Control of absorption is demonstrated by the ability to discontinue drug administration by removing the drug from the skin and by the development of drug delivery devices that can modify the amount of drug allowed onto the skin.\textsuperscript{5} Furthermore, multiple skin sites are available for transdermal drug delivery; thus, local irritation and toxicity can be avoided. Finally, transdermal drug delivery systems offer a method to improve patient compliance and participation because of a decreased systemic toxicity and the opportunity to apply a patch once daily with no further worry or concern. This latter feature may be especially important for patients with hypertension, especially previously asymptomatic persons who have difficulty remembering to take oral medications. Thus, transcutaneous drug delivery may be best for a potent drug with a wide therapeutic window in which first-pass hepatic biotransformation must be avoided. The drug should be potent enough that only small amounts are needed for topical application, and it should have a wide therapeutic range to avoid differences in efficacy and development of toxicity due to variability in absorption.\textsuperscript{14} 

\textbf{Disadvantages.}—The disadvantages of transcutaneous drug delivery include the potential for localized irritant and allergic cutaneous reactions, systemic toxicity, and difficulties associated with the time necessary for a drug to diffuse through the skin. Simple cutaneous irritation can involve local inflammation precipitated by the active agent or the delivery device. Allergic cutaneous reactions may involve mast cell-mediated (mediate) or delayed-type (cell mediated-lymphocyte) hypersensitivity reactions.\textsuperscript{13} A difficulty is the interpretation of the exact cause of the local cutaneous irritation or the allergic hypersensitivity (or both) because transcutaneous drug delivery can expose the skin to multiple compounds, including any vehicles, penetration enhancers, delivery device membranes, polymers or adhesives, and the drug molecule itself. Changing the site of delivery may alleviate the problem, but the potential for continued skin irritation remains. If the local irritation or allergy is in fact due to the delivery device or to the compounds that constitute the delivery system, then alternative methods of drug delivery (such as enteral or parenteral) should eliminate recurrence of the cutaneous reaction. In addition, similar reactions caused by the active agent itself would not be expected to occur with alternative methods of delivery; however, allergic reactions may recur in the skin on rare occasions. An allergic reaction can be further identified by epicutaneous patch testing.

Theoretically, the frequency of hypersensitivity associated with transcutaneous drug delivery should be equal to that associated with drugs delivered by traditional routes and should be relatively low. The potential for systemic toxicity of any drug delivered transdermally is the same as that by traditional routes. For example, transdermal estradiol therapy for postmenopausal symptoms is associated with an increased risk of endometrial carcinoma, as is oral administration of this estrogen.\textsuperscript{1} In addition, overdose is theoretically possible with any drug by applying the drug to multiple skin sites concurrently or by administering it to a wide surface area. Maintaining effective control of transdermal drug delivery may be difficult because of the diffusion time necessary to penetrate the skin. Diffusion of a drug through the stratum corneum can take a considerable amount of time, and the formation of a drug reservoir within the epidermis has been demonstrated.\textsuperscript{8} If a substantial amount of drug builds up within the skin during delivery, the drug may then be subjected to light, bacterial, and enzymatic degradation to generate active or inactive metabolites.\textsuperscript{5,13,16,18} Each of these factors may be involved in the final pharmacokinetic profile of drug delivery through the skin.

\textbf{PRACTICAL CONSIDERATIONS IN TRANSCUTANEOUS DRUG DELIVERY}

\textbf{Factors That Affect Absorption.}—After a decision has been made to use transcutaneous drug delivery, clinicians and
patients should be aware of several practical considerations. For patients, one of the most frequent concerns is whether the site of drug application alters the effectiveness of the drug. Wester reported that the rate of absorption of hydrocortisone was greatest in the areas of the head, neck, axilla, and scrotum and least in the sole of the foot. Although not all drugs have the same degree of absorption as hydrocortisone, the relative ratio of absorption at various skin sites (Fig. 3) is likely similar and correlates with the thickness and lipid content of the stratum corneum. Patients may believe that scopolamine patches are placed behind the ear to affect the vestibular mechanisms within the inner ear, but, in fact, the high absorption of the skin of the head and neck justifies such placement. Individual proprietors usually make recommendations about the application of their product, and this information typically entails placement on the trunk or proximal extremities where absorption rates are similar. Of note, the areas of greatest transcutaneous absorption are also those subjected to the greatest application of cosmetics, antiperspirants, and deodorants.

Another issue about skin site is whether hair or shaving the site before drug application affects absorption. Absorption occurs within the hair follicles and sweat glands, but the contribution beyond short-term diffusion times is negligible. With respect to shaving the skin site, if removing the hair improves adhesion of a delivery device, absorption may be positively affected. Additionally, a particularly harsh shave may remove a substantial number of layers of stratum corneum and thus facilitate absorption. Patients may ask whether cleansing the skin affects drug activity. When a drug that is suspended in an ointment or paste is applied, the simple process of removing the drug from the skin will cease further diffusion. Nonetheless, Wester and Maibach reported that cleansing the skin 24 hours after application enhanced drug delivery, an outcome that was the opposite of what was expected. They suggested that the increased hydration of the skin from the water and detergents facilitated further diffusion of the drug already partitioned within the layers of the epidermis. Thus, these effects would also be expected with cleansing before application. In fact, the proprietors of at least two available transdermal drug delivery systems—namely, those for scopolamine and fentanyl citrate—specifically recommend against cleansing with soaps and detergents to avoid influencing absorption kinetics. Increasing skin hydration is known to enhance transcutaneous absorption and is the basis for the use of occlusive, impermeable saran-wrap type backing of dressings and drug delivery devices.

A final consideration about various skin sites for transdermal drug absorption is the effect of changing the site of the drug during therapy. Generally, after a drug or delivery device has been removed from the skin, the decrease in absorption at the old site is balanced by absorption at the new site if the two sites have comparable absorption rates. Therefore, blood levels of a drug will remain relatively constant.

The effects of other variables such as age, race, and gender on transcutaneous drug absorption are less clear. For example, the effects of age have been examined only in extremely young and elderly patients. The skin of premature infants is considerably more permeable to external chemical absorption in comparison with that of term infants because the barrier function of the skin of premature infants is not yet completely developed. Unfortunately, early evidence of this permeability initially manifested with the use of hexachlorophene, a compound once used to disinfect the skin of premature infants. Hexachlorophene absorbed through the skin of neonates and caused myelinopathy. The skin of term infants seems to have the barrier capability of adult
skin; however, future developments of transdermal drug delivery systems must consider the increased relative surface area of children to that of adults and its effects on overall absorption levels. Transcutaneous drug absorption differences in the elderly population are less clear. A study by Klein and colleagues examined the need for larger surface areas of drug delivery to obtain equal plasma concentrations of clonidine hydrochloride in comparison with a younger population. This finding may result in the need for age-specific transdermal delivery devices.

Variations in absorption among races are the subject of continuing debate. Differences in the physicochemical properties of skin have been demonstrated, such as increased cell adhesion and lipid content in black versus white skin. Wester and Maibach examined the absorption of aspirin, caffeine, and benzoic acid on white, black, and Asian skin and found no differences. Nonetheless, because some chemical compounds show absorption variations among races, a racial difference in transcutaneous absorption could exist and likely depends on the individual drugs examined. Although no formal investigations have compared absorption between genders, Matison hypothesized an increase in transcutaneous absorption of chemicals during pregnancy because of physiologically increased skin hydration and blood flow.

The subject of cutaneous blood flow-related effects is being addressed by researchers. Mechanisms that effectively increase cutaneous blood flow may in fact facilitate drug absorption through the skin by maintenance of the concentration gradient for diffusion. Considerations include fever, exercise, or disorders in autonomic nervous system effects on cutaneous blood flow. The opposite may also be true. For example, Benowitz and coworkers demonstrated decreased transdermal nicotine absorption with concomitant intravenous administration of nicotine and postulated that the vasoconstricting properties of the nicotine may have been responsible. Overall, population studies of transcutaneous delivery are limited, and many practical considerations remain to be elucidated.

Guidelines for Transdermally Delivered Drugs.—Guidelines for the six currently available transdermally delivered drugs (Table 1) are as follows:

1. The device should be applied to clean, nonirritated skin.
2. The site can be cleansed with a dry cloth; the use of water or detergents should be avoided.
3. The device should be applied to a region that has the least amount of hair possible; otherwise, hair may be clipped rather than shaved.
4. Each subsequent dose should be placed at a different site, preferably the corresponding site on the opposite side of the body.

5. Skin irritation indicates the need to change the site; continued skin irritation may necessitate an alternative route of drug delivery.
6. Hypersensitivity may manifest regardless of changing the site and may develop after subsequent oral administration of the same drug.
7. After the drug enters into the general circulation, it is subjected to the same toxicities and drug interactions as when it is administered by traditional routes.

FUTURE DEVELOPMENTS

Future developments of transdermal drug delivery systems will likely focus on the increased control of therapeutic regimens and the continued expansion of drugs available for use. Transdermal drug delivery systems have been considered for use in the development of antihistamines, antihypertensives, antidiabetic, β-blockers, antiemetics, calcium channel antagonists, tranquilizers, antasthmetics, antirretroviral agents, hormones, and centrally acting cholinergic agents. Alternative transdermal drug delivery systems may entail the use of methods such as iontophoresis or phonophoresis. Iontophoresis is the application of an electric current to the skin to facilitate the movement of chemicals through the epidermis. Phonophoresis serves to enhance the absorption of large polar molecules and peptides such as insulin. In addition, iontophoresis provides the opportunity to incorporate electronic control of the rate of drug delivery. Phonophoresis uses ultrasonic irradiation to increase transcutaneous drug absorption. Its effectiveness has not yet been proved conclusively, but further investigations are in progress. Finally, the customization of drug vehicles and enhancers may prove to be the most promising future direction for transdermal drug delivery. As the knowledge of the physicochemical properties and metabolic capabilities of the skin expands, the ability to incorporate the use of pro-drugs, enzyme inhibitors, or anti-inflammatory agents within the delivery system to exploit the natural metabolic pathways of the skin will become possible.

When the concept of transdermal drug delivery first arose, the hope was that most drugs would be adaptable to this method for therapeutic use. Although the rate of progress has not been as rapid as the early pioneers had imagined, safe and effective transdermal drug regimens have
been developed and used successfully. Perhaps the age of transdermal drug delivery has finally arrived. Clinicians have an opportunity to offer more therapeutic options to their patients to optimize their care.

ACKNOWLEDGMENT
We thank Gail M. Sim for assistance with the preparation of the submitted manuscript.

REFERENCES
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The structure of the stratum corneum has been compared to that of "bricks and mortar"; 10 to 15 layers of flattened cornified cells constitute the bricks, and a lipid-rich intercellular matrix constitutes the mortar. This densely packed cellular and lipid apparatus forms an effective barrier to
TRANSCUTANEOUS ABSORPTION

The generally accepted theory is that transcutaneous absorption occurs through the intercellular lipid mortar rather than through the cellular bricks. The factors that control the absorption of drugs across the skin are related to the classic principles of diffusion across semipermeable membranes that involve each component of the skin. The transcutaneous flow of compounds across the stratum corneum is directly proportional to the concentration gradient and therefore can be attributed to passive diffusion. Highly lipophilic compounds with low molecular weight demonstrate the greatest flow rate through the stratum corneum. Additionally, as the surface area exposed to a drug increases and as the thickness of the epidermis decreases, the rate of transdermal flux increases. For compounds used exclusively for the treatment of a skin condition, passive diffusion into the superficial epidermis may be sufficient. For a drug to be delivered to the general circulation, however, it must not only diffuse through the lipid matrix of the stratum corneum but also traverse the aqueous environment of the remaining underlying epidermal layers and dermis. Highly lipophilic drugs diffuse through the lipid mortar quickly but are slowed when they reach the aqueous layers of the epidermis. The opposite is true for polar hydrophilic compounds; the primary barrier is in fact the outer lipid layers of the stratum corneum. Therefore, the drug must maintain affinity for both lipid and aqueous environments for effective absorption. The oil:water partition coefficient of the drug—that is, its relative solubility in oil versus water—and the polarity of the drug must then be considered. Scientists must approach the development of transdermally delivered drugs with this concept in mind.

Several other physiochemical properties of the drug preparation are factors in the effectiveness of transcutaneous transport, including drug stability or volatility, use of a solvent carrier or vehicle, use of a penetration enhancer, and type of delivery device. A drug should remain on the skin without evaporating or becoming otherwise inactive due to spontaneous chemical breakdown. A simple method to accomplish this situation has been to suspend the drug in a vehicle—an any gel, lotion, or paste used to apply the drug to the skin. Penetration enhancers include several compounds that are mixed into vehicles to alter the molecular environment of the epidermis, most often the lipid mortar of the stratum corneum, and facilitate drug absorption. Finally, the delivery system itself occasionally proves to be the ultimate determinant of transdermal drug flow. A simple patch-type delivery system is shown in Figure 2. The basic system consists of adhesive and a drug reservoir with or without a rate-controlling membrane, all covered by an occlusive backing. Drug-delivery devices have been designed to control the rate of drug diffusion into the skin; they are not used to apply the drug as an ointment or lotion. Each of these factors becomes interdependent in the determination of the final rate of transcutaneous drug delivery. The pharmacokinetics resulting from these interactions may prove to be complex; the methods and models involved are the subject of intense research beyond the scope of most clinicians.

TRANSCUTANEOUS DRUG DELIVERY

Advantages.—Clinically, the decision to use transdermal drug delivery is based on the relative advantages and disadvantages for the patient. Advantages include the following: avoidance of the gastrointestinal (GI) tract and hepatic first-

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pass biotransformation and metabolism, control of absorption, availability of multiple skin sites to avoid local irritation and toxicity, and improved patient compliance. Therapeutic levels of a drug such as nitroglycerin can be achieved with much lower dosages and with tighter control in light of the fact that absorption occurs on a limited area of the skin rather than the drug being exposed to large areas of the GI tract and hepatic first-pass metabolism. Furthermore, the biochemical environment of the GI tract, including the acidic environment of the stomach, the influence of food, and the presence and influence of normal gut flora, can be avoided. Control of absorption is demonstrated by the ability to discontinue drug administration by removing the drug from the skin and by the development of drug delivery devices that can modify the amount of drug allowed onto the skin. Furthermore, multiple skin sites are available for transdermal drug delivery; thus, local irritation and toxicity can be avoided. Finally, transdermal drug delivery systems offer a method to improve patient compliance and participation because of a decreased systemic toxicity and the opportunity to apply a patch once daily with no further worry or concern. This latter feature may be especially important for patients with hypertension, especially previously asymptomatic persons who have difficulty remembering to take oral medications. Thus, transcutaneous drug delivery may be best for a potent drug with a wide therapeutic window in which first-pass hepatic biotransformation must be avoided. The drug should be potent enough that only small amounts are needed for topical application, and it should have a wide therapeutic range to avoid differences in efficacy and development of toxicity due to variability in absorption.

Disadvantages.—The disadvantages of transcutaneous drug delivery include the potential for localized irritant and allergic cutaneous reactions, systemic toxicity, and difficulties associated with the time necessary for a drug to diffuse through the skin. Simple cutaneous irritation can involve local inflammation precipitated by the active agent or the delivery device. Allergic cutaneous reactions may involve mast cell-mediated (mediate) or delayed-type (cell mediated-lymphocyte) hypersensitivity reactions. A difficulty is the interpretation of the exact cause of the local cutaneous irritation or the allergic hypersensitivity (or both) because transcutaneous drug delivery can expose the skin to multiple compounds, including any vehicles, penetration enhancers, delivery device membranes, polymers or adhesives, and the drug molecule itself. Changing the site of delivery may alleviate the problem, but the potential for continued skin irritation remains. If the local irritation or allergy is in fact due to the delivery device or to the compounds that constitute the delivery system, then alternative methods of drug delivery (such as enteral or parenteral) should eliminate recurrence of the cutaneous reaction. In addition, similar reactions caused by the active agent itself would not be expected to occur with alternative methods of delivery; however, allergic reactions may recur in the skin on rare occasions. An allergic reaction can be further identified by epicutaneous patch testing.

Theoretically, the frequency of hypersensitivity associated with transcutaneous drug delivery should be equal to that associated with drugs delivered by traditional routes and should be relatively low. The potential for systemic toxicity of any drug delivered transdermally is the same as that by traditional routes. For example, transdermal estradiol therapy for postmenopausal symptoms is associated with an increased risk of endometrial carcinoma, as is oral administration of this estrogen. In addition, overdose is theoretically possible with any drug by applying the drug to multiple skin sites concurrently or by administering it to a wide surface area. Maintaining effective control of transdermal drug delivery may be difficult because of the diffusion time necessary to penetrate the skin. Diffusion of a drug through the stratum corneum can take a considerable amount of time, and the formation of a drug reservoir within the epidermis has been demonstrated. If a substantial amount of drug builds up within the skin during delivery, the drug may then be subjected to light, bacterial, and enzymatic degradation to generate active or inactive metabolites. Each of these factors may be involved in the final pharmacokinetic profile of drug delivery through the skin.

PRACTICAL CONSIDERATIONS IN TRANSCUTANEOUS DRUG DELIVERY

Factors That Affect Absorption.—After a decision has been made to use transcutaneous drug delivery, clinicians and
patients should be aware of several practical considerations. For patients, one of the most frequent concerns is whether the site of drug application alters the effectiveness of the drug. Wester\textsuperscript{19} reported that the rate of absorption of hydrocortisone was greatest in the areas of the head, neck, axilla, and scrotum and least in the sole of the foot. Although not all drugs have the same degree of absorption as hydrocortisone, the relative ratio of absorption at various skin sites (Fig. 3) is likely similar and correlates with the thickness and lipid content of the stratum corneum.\textsuperscript{20} Patients may believe that scopolamine patches are placed behind the ear to affect the vestibular mechanisms within the inner ear, but, in fact, the high absorption of the skin of the head and neck justifies such placement. Individual proprietors usually make recommendations about the application of their product, and this information typically entails placement on the trunk or proximal extremities where absorption rates are similar. Of note, the areas of greatest transcutaneous absorption are also those subjected to the greatest application of cosmetics, antiperspirants, and deodorants.

Another issue about skin site is whether hair or shaving the site before drug application affects absorption. Absorption occurs within the hair follicles and sweat glands, but the contribution beyond short-term diffusion times is negligible.\textsuperscript{3} With respect to shaving the skin site, if removing the hair improves adhesion of a delivery device, absorption may be positively affected. Additionally, a particularly harsh shave may remove a substantial number of layers of stratum corneum and thus facilitate absorption.\textsuperscript{2} Patients may ask whether cleansing the skin affects drug activity. When a drug that is suspended in an ointment or paste is applied, the simple process of removing the drug from the skin will cease further diffusion. Nonetheless, Wester and Maibach\textsuperscript{21} reported that cleansing the skin 24 hours after application enhanced drug delivery, an outcome that was the opposite of what was expected. They suggested that the increased hydration of the skin from the water and detergents facilitated further diffusion of the drug already partitioned within the layers of the epidermis. Thus, these effects would also be expected with cleansing before application.\textsuperscript{21,22} In fact, the proprietors of at least two available transdermal drug delivery systems—namely, those for scopolamine and fentanyl citrate—specifically recommend against cleansing with soaps and detergents to avoid influencing absorption kinetics.\textsuperscript{23} Increasing skin hydration is known to enhance transcutaneous absorption and is the basis for the use of occlusive, impermeable saran-wrap type backing of dressings and drug delivery devices.\textsuperscript{25}

A final consideration about various skin sites for transdermal drug absorption is the effect of changing the site of the drug during therapy. Generally, after a drug or delivery device has been removed from the skin, the decrease in absorption at the old site is balanced by absorption at the new site if the two sites have comparable absorption rates. Therefore, blood levels of a drug will remain relatively constant.\textsuperscript{13}

The effects of other variables such as age, race, and gender on transcutaneous drug absorption are less clear. For example, the effects of age have been examined only in extremely young and elderly patients. The skin of premature infants is considerably more permeable to external chemical absorption in comparison with that of term infants because the barrier function of the skin of premature infants is not yet completely developed.\textsuperscript{2} Unfortunately, early evidence of this permeability initially manifested with the use of hexachlorophene, a compound once used to disinfect the skin of premature infants. Hexachlorophene absorbed through the skin of neonates and caused myelinopathy.\textsuperscript{24} The skin of term infants seems to have the barrier capability of adult
skin; however, future developments of transdermal drug delivery systems must consider the increased relative surface area of children to that of adults and its effects on overall absorption levels.\textsuperscript{2} Transcutaneous drug absorption differences in the elderly population are less clear. A study by Klein and colleagues\textsuperscript{23} of elderly patients demonstrated the need for larger surface areas of drug delivery to obtain equal plasma concentrations of clonidine hydrochloride in comparison with a younger population. This finding may result in the need for age-specific transdermal delivery devices.

Variations in absorption among races are the subject of continuing debate. Differences in the physiochemical properties of skin have been demonstrated, such as increased cell adhesion and lipid content in black versus white skin.\textsuperscript{26} Wester and Maibach\textsuperscript{27} examined the absorption of aspirin, caffeine, and benzoic acid on white, black, and Asian skin and found no differences. Nonetheless, because some chemical compounds show absorption variations among races, a racial difference in transcutaneous absorption could exist and likely depends on the individual drugs examined.\textsuperscript{25} Although no formal investigations have compared absorption between genders, Mattison\textsuperscript{26} hypothesized an increase in transcutaneous absorption of chemicals during pregnancy because of physiologically increased skin hydration and blood flow.

The subject of cutaneous blood flow-related effects is being addressed by researchers. Mechanisms that effectively increase cutaneous blood flow may in fact facilitate drug absorption through the skin by maintenance of the concentration gradient for diffusion.\textsuperscript{16} Considerations include fever, exercise, or disorders in autonomic nervous system effects on cutaneous blood flow. The opposite may also be true. For example, Benowitz and coworkers\textsuperscript{25} demonstrated decreased transdermal nicotine absorption with concomitant intravenous administration of nicotine and postulated that the vasoconstricting properties of the nicotine may have been responsible. Overall, population studies of transcutaneous delivery are limited, and many practical considerations remain to be elucidated.

**Guidelines for Transdermally Delivered Drugs.**—Guidelines for the six currently available transdermally delivered drugs (Table 1) are as follows:

1. The device should be applied to clean, nonirritated skin.
2. The site can be cleansed with a dry cloth; the use of water or detergents should be avoided.
3. The device should be applied to a region that has the least amount of hair possible; otherwise, hair may be clipped rather than shaved.
4. Each subsequent dose should be placed at a different site, preferably the corresponding site on the opposite side of the body.

<table>
<thead>
<tr>
<th>Table 1.—Currently Available Medications for Transcutaneous Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine hydrochloride\textsuperscript{3,2,30}</td>
</tr>
<tr>
<td>Scopolamine\textsuperscript{1,2,3,11}</td>
</tr>
<tr>
<td>Estradiol\textsuperscript{1,2,12}</td>
</tr>
<tr>
<td>Fentanyl citrate\textsuperscript{1,2,3,33}</td>
</tr>
<tr>
<td>Nitroglycerin\textsuperscript{1,2,3,34}</td>
</tr>
<tr>
<td>Nicotine\textsuperscript{1,2,3,35}</td>
</tr>
</tbody>
</table>

5. Skin irritation indicates the need to change the site; continued skin irritation may necessitate an alternative route of drug delivery.

6. Hypersensitivity may manifest regardless of changing the site and may develop after subsequent oral administration of the same drug.

7. After the drug enters into the general circulation, it is subjected to the same toxicities and drug interactions as when it is administered by traditional routes.

**FUTURE DEVELOPMENTS**

Future developments of transdermal drug delivery systems will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal drug delivery systems have been considered for use in the development of antihistamines, antihypertensives, antiadrenergics, β-blockers, antiemetics, calcium channel antagonists, tranquilizers, antasthmatics, antiretroviral agents, hormones, and centrally acting cholinergeic agents.\textsuperscript{3,36,37} Alternative transdermal drug delivery systems may entail the use of methods such as iontophoresis or phonophoresis. Iontophoresis is the application of an electric current to the skin to facilitate the movement of chemicals through the epidermis.\textsuperscript{38,39} Iontophoresis serves to enhance the absorption of large polar molecules and peptides such as insulin.\textsuperscript{39} In addition, iontophoresis provides the opportunity to incorporate electronic control of the rate of drug delivery. Phonophoresis uses ultrasonic irradiation to increase transcutaneous drug absorption. Its effectiveness has not yet been proved conclusively, but further investigations are in progress.\textsuperscript{30,41} Finally, the customization of drug vehicles and enhancers may prove to be the most promising future direction for transdermal drug delivery. As the knowledge of the physicochemical properties and metabolic capabilities of the skin expands, the ability to incorporate the use of pro-drugs, enzyme inhibitors, or anti-inflammatory agents within the delivery system to exploit the natural metabolic pathways of the skin will become possible.

When the concept of transdermal drug delivery first arose, the hope was that most drugs would be adaptable to this method for therapeutic use. Although the rate of progress has not been as rapid as the early pioneers had imagined, safe and effective transdermal drug regimens have
been developed and used successfully. Perhaps the age of transdermal drug delivery has finally arrived. Clinicians have an opportunity to offer more therapeutic options to their patients to optimize their care.

ACKNOWLEDGMENT
We thank Gail M. Sim for assistance with the preparation of the submitted manuscript.

REFERENCES
TOPICAL SECRETIN for the Treatment of AUTISM

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Autistic children exhibit sensory disturbances, specific forms of social impairment, repetitive behaviors, communication and cognitive deficits, an abnormal nutrition profile, and (usually) a compromised immune system.1 Many also suffer from sleep disturbances, poor digestion, malabsorption, seizures, and an overgrowth of viruses, pathogenic bacteria, yeast, and/or parasites in the gut. Research1 has indicated that the gastrointestinal tract, the immune system, and the brain are affected by this disorder. Various theories1 have implicated pertussis toxin or ethylmercury in certain vaccines as etiologic factors, but no cause has been definitively identified.

Studies1 have shown that autistic children do not release secretin, which enables the release of bicarbonate in the small bowel and may help to increase the availability of serotonin. The following case reports illustrate the effect of treatment with topical secretin in ameliorating the symptoms of autism in two pediatric patients.

CASE REPORT 1

A 5 1/2-year-old boy treated by our practice was diagnosed as having autism at 2 1/2 years of age. Some studies2 indicate that the siblings of autistic children may also carry the gene for autism; however, the siblings of this patient are not autistic. When he was 4 years of age, the patient’s physician initiated treatment with intravenous infusions of porcine-derived secretin, which is a neurotransmitter and polypeptide composed of 27 amino acids.3 Secretin is one of the hormones that controls digestion by stimulating the pancreas to release digestive fluids rich in bicarbonate, which neutralizes acidity in the intestines.3 The infusions of secretin, which were administered every 5 to 6 weeks, were very traumatic for the patient and his family. However, that treatment produced an improvement in his physical health and behavior that was noted by his parents and teachers. Eventually, the porcine secretin used for intravenous administration became unavailable because of a shortage in supply, and the patient’s therapy was terminated.

Before he underwent treatment with intravenous porcine-derived secretin, this patient had exhibited severe, uncontrollable tantrums and usually spoke in requests expressed in three or four words when prompted or when the Picture Exchange Communication System (PECS),4 a training package that enables those with nonverbal skills to initiate communication, was used. He was restless, distracted, and unable to concentrate on one task at a time. He slept from 8:00 pm to 4:30 am, usually without waking.

This patient followed a gluten-free and casein-free (GFCF) very restricted diet and had been taking the nutritional supplement d-methylglycine (DMG), which is available only in tablet form, as well as Ethex and multivitamins. The patient’s physician asked us to compound the DMG into a fruit-flavored liquid that could be added to juice for administration.

On February 23, 1999, this patient’s physician prescribed human secretin 2 clinical units /0.1 mL in Pluronic lecithin organogel (PLO) to be dispensed in 1-mL syringes with increment markings for each 0.1 mL. Every night before the patient went to bed, one of his parents wore a glove or a finger cot and rubbed 0.1 mL (2 clinical units) on his leg. Two days after therapy was initiated, the patient slept from 8:00 pm until 7:00 am without waking. When he was evaluated 1 month after the initiation of therapy, he had exhibited a dramatic decrease in the frequency and severity of his tantrums and was sleeping until 6:30 am without waking. Two months after the initiation of treatment with topical human secretin, his teachers reported that his ability to learn in school had greatly progressed. Three months after the initiation of therapy, he exhibited improved concentration and a reduction in the number of tantrums.

At the time of this writing and as a result of continuing treatment with topical human secretin, this patient’s behavior and attention span have improved even more. He can concentrate enough to watch an entire movie, can be read to by his parents, and responds more appropriately to questions. His restricted diet is unchanged, and he gained 2 pounds during his 4 months of treatment. His vocabulary continues to improve as it did before therapy was initiated, but he is more willing to work on pronunciation. The number and severity of his tantrums have continued to decrease.

This patient now attends a mainstream school; his classmates are not autistic. After school, an aide provides assistance at his home. His therapy with a constant dose of topical human secretin has been maintained since the initiation of treatment, and he has experienced no side effects as a result of therapy.

CASE REPORT 2

A 7-year-old boy with celiac disease was diagnosed as being autistic when he was 3 years of age. When the patient was 5 years old, treatment with intravenous infusions of porcine secretin was initiated. After he had received an infusion of secretin, the patient’s behavior would improve for 1 or 2 weeks, after which he would regress during the next 4 to 5 weeks until the next infusion was administered. When he was not receiving secretin, he exhibited a short attention span, poor language development, occasional hyperactivity, trouble sleeping through the night, poor appetite, and an inconsistent pattern of bowel movements. During the previous year, he had gained only 3 or 4 pounds. The patient’s treatment regimen included DMG and a multivitamin, as well as additional vitamin B complex, folic acid, and magnesium. His physician prescribed human secretin 2 clinical units /0.1 mL in Pluronic lecithin organogel (PLO) to be dispensed in 1-mL syringes, and his parents were instructed to wear a glove or a finger cot and to rub 0.1 mL (2 clinical units) every night at bedtime into his calf, his buttck, the top of his foot, or his back.

At one point during his therapy, the patient’s treatment with topical human secretin was interrupted for more than 2 weeks because his parents could not afford its purchase. Within 3 to 4 days after the termination of treatment, he regressed emotionally and experienced digestive problems. He became hyperactive,
noncompliant, cried and screamed without provocation, and became severely constipated. Treatment was then resumed, and by the second day, the patient’s condition had improved. During the next 3 days he became calm, his attention span and concentration improved, he spoke more intelligibly, and his normal pattern of bowel movements resumed.

During his treatment with topical human secretin (except for the 2 weeks during which therapy was interrupted), this patient experienced a remarkable improvement in his behavior and learning abilities. Since daily treatment with human secretin in PLO was resumed, he has not regressed. He has never experienced side effects from therapy. His pattern of bowel movements has improved 50% to 70%, he is calmer, his attention span and ability to concentrate are greater, and he participates in family functions. He speaks in short sentences; this is a 50% improvement in his pattern of speech (before treatment he spoke only single words). He now asks his mother to read to him, which he had not requested before treatment.

Since therapy with secretin was resumed, this patient has exhibited behavior that is more normal for his age. When he began to attend kindergarten in the autumn of 2000, his teachers were amazed at his improved behavior, learning skills, and social progress. As a result of that improvement, he now attends a mainstream school and is assisted by an aide. His parents are delighted with his progress, and they now enjoy many activities together.

REFERENCES


SUGGESTED READING

Selegiline Hydrochloride 10 mg/mL in Pluronic Lecithin Organogel

Rx

For 100 mL
Selegiline hydrochloride 1 g
Purified water 5 mL
Lecithin and isopropyl palmitate solution 22 mL
Pluronic F127 20% gel qs 100 ml

METHOD OF PREPARATION
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Dissolve the selegiline hydrochloride in the purified water.
4. Incorporate the solution into about 70 mL of the Pluronic F127 20% gel and mix well.
5. Incorporate the lecithin and isopropyl palmitate solution and mix well, using a high-shear mixing method.
6. Incorporate sufficient Pluronic F127 20% gel to volume and continue mixing, using a high-shear mixing method.
7. Package and label.

Note: The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g sorbic acid, 20 g of Pluronic F127 and sufficient purified water to make 100 mL.

PACKAGING
Package in a tight, light-resistant container.

LABELING
For external use only. Use only as directed. Keep out of reach of children.

STABILITY
A beyond-use date of 14 days would be appropriate for this preparation.

USE
Selegiline hydrochloride in Pluronic lecithin organogel has been used in the treatment of Parkinson’s disease and other conditions of cognitive impairment.

QUALITY CONTROL
Quality-control tests can include theoretical weight compared to actual weight, specific gravity, active-drug assay, rheological properties and physical observations.

DISCUSSION
Selegiline hydrochloride is a relatively stereoselective monoamine oxidase-B inhibitor used as orally administered 5-mg capsules or tablets in the symptomatic treatment of Parkinsonian syndrome. A number of studies have reported the pharmacokinetics, effectiveness and safety of transdermally administered selegiline. The advantages of transdermal administration are increased blood levels of the drug and decreased blood levels of metabolites, indicating that extensive first-pass effect is avoided by topical administration.

Selegiline hydrochloride (C13H17N.HCl, MW 223.74) occurs as a white, odorless, crystalline powder that is freely soluble in water. It has a pKa of 7.5 and melts at 141 to 145°C.

Purified water is water that is obtained by distillation, ion exchange, reverse osmosis or some other suitable process.

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex derived from vegetable sources. Lecithin is practically insoluble in water, polar solvents and cold vegetable and animal oils; however, when mixed with water, it hydrates to form emulsions.

Isopropyl palmitate (C19H38O2, MW 298.51) is a colorless, mobile liquid that is soluble in acetone, castor oil, cottonseed oil, alcohol and mineral oil. It is insoluble in water, glycerin and propylene glycol.

Pluronic F127 is generally available in powdered form. It is either odorless or may have a very mild odor. It is freely soluble in water, alcohol and isopropyl alcohol.

REFERENCES
Testosterone 1 mg/0.1 mL Pluronic Lecithin Organogel (PLO)

**Rx**

For 100 mL:
- Testosterone 1 g
- Ethoxy diglycol or propylene glycol 3 g
- Lecithin and isopropyl palmitate solution 22 mL
- Pluronic F127 20% solution qs 100 mL

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Accurately weigh and/or measure each ingredient.
3. Mix the testosterone with the ethoxy diglycol or propylene glycol and form a smooth paste.
4. Incorporate the lecithin and isopropyl palmitate mixture and mix until uniform.
5. Add sufficient Pluronic F127 20% aqueous solution to volume and mix by means of a high-shear mixing method.
6. Package and label.

   **Note:** The lecithin:isopropyl palmitate solution can be prepared by mixing 0.2 g of sorbic acid, 50 g of soy lecithin, and 50 g of isopropyl palmitate. The Pluronic F127 solution can be prepared by mixing 0.2 g of sorbic acid, 20 g of Pluronic F127, and sufficient purified water to make 100 mL.

**PACKAGING**

Package in tight, light-resistant containers.

**LABELING**

Use only as directed. For topical use only.

**STABILITY**

A beyond-use date of 6 months can be used for this preparation.

**USE**

Testosterone in Pluronic-lecithin organogel (PLO) has been used in male hormone replacement therapy and to enhance libido in women. It should not be applied vaginally.

**QUALITY CONTROL**

Actual yield compared to theoretical yield, physical observation.

**DISCUSSION**

Testosterone occurs as white or slightly creamy white crystals or crystalline powder that is odorless and stable in air. It is practically insoluble in water and is soluble 1 g in 5 mL of ethanol, in 2 mL of chloroform, and in 100 mL of ether. It is soluble in vegetable oils. It melts between 153°C and 157°C. Testosterone is subject to photodegradation in the presence of light. It is indicated as androgen replacement for delayed male puberty and for the treatment of postpartum breast pain and engorgement, inoperable breast cancer, and male hypogonadism.\(^2\)\(^-\)\(^4\)

Ethoxy diglycol \((C_2\text{H}_4\text{O}_2\text{H})\), \(CH_2\text{OHCCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{H}_2\), diethylene glycol monoethyl ether, diethylene glycol ethyl ether, Carbitol, Transcutol, MW 134.20. It occurs as a colorless liquid with a mild pleasant odor. It is hygroscopic and is miscible with water and with common organic solvents.\(^5\)

Propylene glycol \((C_3H_8O_2)\) occurs as a clear, colorless, viscous, practically odorless liquid with a sweet taste resembling that of glycerin. It has a specific gravity of 1.038 g/mL and is miscible with each of the following: acetone, chloroform, 95% ethanol, glycerin, and water. Propylene glycol is actually a better solvent than glycerin. Because propylene glycol is hygroscopic, it should be stored in an airtight container and protected from light. Incompatibilities include potassium permanganate.\(^6\)

Lecithin (egg lecithin, soybean lecithin, vegetable lecithin) describes a complex mixture of acetone-insoluble phosphatides. The composition and physical properties vary according to the source of the lecithin and the degree of purification. Lecithin derived from vegetable sources has a bland or nut-like taste and varies from brown to light yellow, depending on whether the source was bleached or unbleached. Lecithin should be stored in a well-closed container and protected from light.\(^7\)

Isopropyl palmitate \((C_{39}H_{68}O_2, MW 298.51)\) is a colorless mobile liquid with a very slight odor that is used as an emollient, an oleaginous vehicle, and a solvent. It has good spreading characteristics. It is soluble in each of the following: acetone, castor oil, cottonseed oil, alcohol, and mineral oil. It is insoluble in water, in glycerin, and in propylene glycol. It should be stored in a well-closed container and protected from light.\(^8\)

Pluronic F127, a poloxamer, is freely soluble in water, in alcohol, and in isopropyl alcohol. Poloxamers are usually white, waxy, free-flowing granules or cast solids that are practically odorless and tasteless.\(^9\)

**References**

Tretinoin and (-)Alpha-Bisabolol Gel

**Rx**

<table>
<thead>
<tr>
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<th>For 100 g</th>
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<tbody>
<tr>
<td>Tretinoin</td>
<td>50 mg</td>
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<tr>
<td>(-)Alpha-bisabolol</td>
<td>100 mg</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>5 g</td>
</tr>
<tr>
<td>Cremophor RH400</td>
<td>6 g</td>
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<tr>
<td>Butylated hydroxytoluene</td>
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<td>Methylparaben</td>
<td>200 mg</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>50 mg</td>
</tr>
<tr>
<td>Pluronic F-127</td>
<td>18.5 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>70.3 g</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**
1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Heat the purified water to about 75°C and dissolve the parabens; cool to about 40°C.
4. Mix the tretinoin, PEG 40, Cremophor RH400, butylated hydroxytoluene, and (-)alpha-bisabolol and heat to about 40°C; stir until dissolved.
5. Add the aqueous phase to the oil phase.
6. Heat the mixture to about 50°C, dissolve about 14 g of the Pluronic F-127, and mix well.
7. Cool to about 6°C, add the remainder of the items and sufficient purified water to volume, and mix well. Keep the mixture in a cool temperature until the air bubbles have escaped.
8. Package and label.

**PACKAGING**
Package in tight, light-resistant containers.1

**LABELING**
Keep out of reach of children. Use only as directed.

**STABILITY**
A beyond-use date of up 6 months can be used for this preparation.1

**USE**
This preparation is used in the treatment of various skin disorders.

**QUALITY CONTROL**
Quality-control assessment can include theoretical weight compared to actual weight, pH, specific gravity, active drug assay, color, texture-surface, texture-spatula spread, appearance, feel, rheological properties, and physical observations.2

**DISCUSSION**
Tretinoin (C₂₀H₂₈O₂, MW 222.4) occurs as a yellow to light-orange crystalline powder that is insoluble in water, slightly soluble in alcohol, and sensitive to light, heat, and air. Tretinoin is used primarily in the topical treatment of acne vulgaris and various neoplastic and related skin disorders, to include rosacea.3

(-)Alpha-bisabolol (C₁₅H₂₆O, MW 222.4, Levomenol) is a sesquiterpene isolated from the volatile oil of chamomile. It is present in many emollient preparations and is used as a penetration enhancer.3

Polyethylene glycol 400 (Carbowax, PEG) occurs as a clear, colorless, or slightly yellow-colored viscous liquid with a slight, but characteristic odor and a bitter, slightly burning taste. It is soluble in water and miscible with other PEGs.4

Cremophor RH400 occurs as a white to yellowish semisolid paste at 20°C that liquifies at 30°C. It has a very faint characteristic odor and is almost tasteless in aqueous solutions.5

Butylated hydroxytoluene (BHT) is an antioxidant that occurs as a white or pale yellow crystalline solid or powder with a faint characteristic odor that is practically insoluble in water, glycerin, propylene glycol, solutions of alkali hydroxides, and dilute aqueous mineral acids.6

Methylparaben (C₇H₈O₃, MW 152.1, methyl hydroxybenzoate, methyl parahydroxybenzoate), an antimicrobial preservative, is available as colorless crystals or as a white, crystalline powder that is odorless, or almost odorless, and has a slight burning taste. One gram is soluble in 400 mL of water and 3 mL of 95% ethanol.7

Propylparaben (C₇H₈O₃, MW 180.20, propyl parahydroxybenzoate), antimicrobial preservative, is available as a white, crystalline, odorless, and tasteless powder. One gram is soluble in 2500 mL of water and 1.1 mL ethanol.7

Pluronic F-127, generally available in powdered form, is one of the poloxamers, which are used as emulsifying, solubilizing, and wetting agents that are available in different grades. They generally are white-colored, waxy, free-flowing granules or as cast solids that are practically odorless and tasteless. It is freely soluble in water, alcohol, and isopropyl alcohol.8

**REFERENCES**