Development and Characterization of Lidocaine Transdermal System with *In-Situ* Self-Emulsifying Nanosystem (*i-SENS*)

International Conference and Expo on Biopharmaceutics

**Presented By:**
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Ascent Pharmaceuticals Inc.
OBJECTIVE

The objective of this work is to develop and characterize \textit{in-situ} Self-Emulsifying Nanosystem (\textit{i-SENS}) based Lidocaine Transdermal System having Lidocaine in Nano-emulsion form.

\textbf{Fig 1: i-SENS Transdermal System}
INTRODUCTION

- Patient compliance
- Easy to use and noninvasive
- Easy to modulate the drug release rate
- Long-term duration
- Poor oral absorption drugs
- High drug load
- Stable

Figure 2: Conceptual Diagram of i-SENS TDS
INTRODUCTION

Self-Emulsifying Nanosystem (SENS) – isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants that can be used for the design of formulations in order to improve the absorption of highly lipophilic drug compounds

Advantages:
• Solubility
• Bioavailability
• Dissolution Rate
• Thermodynamically Stable
• Enhances therapeutic efficacy

Importance of SENS:
• Improve transdermal permeation
• Surfactants act as penetration enhancers
• High solubilization capacity

Examples: gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin and nimesulide
Fig 3: Technology Extension
INTRODUCTION

Transdermal Drug Delivery System

Advantages
• Biological half-lives
• Therapeutic value
• Avoid first pass effect
• Patient compliance
• Easy to use and noninvasive
• Controlled release
• Long-term duration
• Poor oral absorption drugs

Disadvantages
• Low molecular weight compounds
• Skin irritation
• Uncomfortable
• Environmental Conditions
• Stratum corneum as barrier
• Not economical
Introduction

Lidocaine:

- Local anesthetic and cardiac depressant used as an antiarrhythmia agent.

Physiochemical Properties of Lidocaine

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>$\text{C}<em>{14}\text{H}</em>{22}\text{N}_2\text{O}$</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>234.33728 g/mol</td>
</tr>
<tr>
<td>Color</td>
<td>White or Slightly Yellow, crystalline powder</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>159-160 °C at 2.00E+00 mm Hg</td>
</tr>
<tr>
<td>Melting Point</td>
<td>68 °C</td>
</tr>
<tr>
<td>Solubility</td>
<td>Very soluble in alcohol, chloroform; freely soluble in ether, benzene and</td>
</tr>
<tr>
<td></td>
<td>dissolves in oils</td>
</tr>
<tr>
<td>pKa</td>
<td>8.01</td>
</tr>
</tbody>
</table>
Methods and Experiments

Fig 5: Flow diagram showing the steps of Manufacturing

SENS Preparation

i-SENS TDS BASE Preparation

i-SENS Coating on Felt

bulk ware

slit lengthwise into

punch and package patches/strips out of daughter coils
Introduction

Phase Diagram

![Phase Diagram Image]

- Stable Nanoemulsion
- Unstable Nanoemulsion
- Macroemulsion

Fig 6: Phase Diagram
Preparation of *in-Situ* Self-Emulsifying NanoSystem (*i*-SENS):

Lidocaine *i*-SENS was prepared by dissolving Lidocaine in a hydrophilic, lipophilic, surfactant and co-surfactant matrix. The resultant was a clear isotropic mixture.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredient</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lidocaine</td>
<td>API</td>
</tr>
<tr>
<td>2</td>
<td>1, 3 butanediol</td>
<td>Solubilizer</td>
</tr>
<tr>
<td>3</td>
<td>Cremophore EL</td>
<td>Surfactant</td>
</tr>
<tr>
<td>4</td>
<td>Capmol MCM</td>
<td>Solubilizer</td>
</tr>
</tbody>
</table>
Preparation of Transdermal patches containing *i*-SENS:

Lidocaine *i*-SENS was added to a base to create a formulation for a transdermal system. This formulation was coated on a felt using the Optimags Coating Machine with optimized parameters.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredient</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium Polyacrylate</td>
<td>Polymer</td>
</tr>
<tr>
<td>2</td>
<td>1,3 Butylene Glycol</td>
<td>Solubilizer</td>
</tr>
<tr>
<td>3</td>
<td>Dihydroxyaluminum Aminoacetate</td>
<td>Cross linking agent</td>
</tr>
<tr>
<td>4</td>
<td>Disod. EDTA</td>
<td>Chelating agent</td>
</tr>
<tr>
<td>5</td>
<td>D-Sorbitol</td>
<td>Humectant</td>
</tr>
<tr>
<td>6</td>
<td>Gelatin</td>
<td>polymer</td>
</tr>
<tr>
<td>7</td>
<td>Kaolin Colloidal USP</td>
<td>Emollient</td>
</tr>
<tr>
<td>8</td>
<td>Methylparaben</td>
<td>Preservative</td>
</tr>
<tr>
<td>9</td>
<td>Propylparaben</td>
<td>Preservative</td>
</tr>
<tr>
<td>10</td>
<td>Polysorbate 80</td>
<td>Solubilizer</td>
</tr>
<tr>
<td>11</td>
<td>Povidone k90</td>
<td>Polymer</td>
</tr>
<tr>
<td>12</td>
<td>Propylene Glycol</td>
<td>Plasticizer</td>
</tr>
<tr>
<td>13</td>
<td>Sod. CMC</td>
<td>Polymer</td>
</tr>
<tr>
<td>14</td>
<td>Tartaric Acid</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>15</td>
<td>Titanium Dioxide</td>
<td>Coating agent, opacifier</td>
</tr>
</tbody>
</table>
Methods and Experiments

Fig 7: Coating Machine
Methods and Experiments

Fig 8: Harro Hofliger Packaging Machine

Ascent Pharmaceuticals Inc. Drug Delivery Center
Methods and Experiments

Fig 9: *i-SENS Transdermal Patch:*

Fig 10: Physically Bonded SENS Network in Polymer

Fig 11: Microphotograph of *i-SENS Transdermal Patch Gel*
MECHANISM OF ACTION

Drug Release Stages:
1. Drug release from formulation
2. Diffusion across SC via intercellular & intracellular
3. Transfer from SC to epidermis
4. Systemic circulation via capillary network

Figure 12: i-SENS TDS Mechanism of Action
Methods and Experiments

*i-SENS* Lidocaine TDS

Control

Fig 13: Patches
Methods and Experiments

Optimization DoE for formulation variables
• A Box Behnken DoE with randomized runs was generated to map the effects of different formulation variables.

Variables

Polymer/Cross-linking agent/Chelator

• Drug Release
• Moisture Level
• Viscosity
• Peel Strength

Figure 14: Box-Optimization DoE for investigating the effect of formulation variables
Methods and Experiments

Lidocaine i-SENS

• **Transmittance** – Using a UV Spectrophotometer, absorbance spectra of various compounds can be measured

• **Emulsification Rate** – Preparing a solution of API and excipients in a water immiscible solvent which is emulsified into an aqueous surfactant solution. The solvent is removed from emulsion droplets to form particles

• **Viscosity** – Brookfield Viscometer measures fluid viscosity at given shear rates. The principal of operation is to drive a spindle through a calibrated spring.
Methods and Experiments

Lidocaine i-SENS

• **Water Uptake Study** – Percentage of water uptake can be calculated by measuring how much water can be added to 1 gram of fill material until precipitate is formed.

• **Potency** – Drug content was found by making a 1000 ppm solution and further diluting it and measuring absorbance using UV spectrophotometer

• **Stability** – Conducted to observe the influence of temperature and relative humidity on the drug content
Methods and Experiments

Transdermal System

• **Description** – 10 cm x 14 cm Patch

• **Thickness** – The thickness of the film was measured using electronic vernier calipers. Measurements were taken at five different points on the film and the average of these readings were taken

• **Percentage of Moisture Content** – The prepared formulation was kept in the Ohaus machine and percent moisture content was calculated

• **Cold Flow** – Caused by the viscoelastic creep of the adhesive layer

• **Content Uniformity** – 10 patches are selected and content is determined for individual patches. The transdermal patches pass the test if they fall in a specific range
Methods and Experiments

Transdermal System

• **Folding Endurance** – It was determined by repeatedly folding the film at the same place until it breaks or cracking has been observed

• **Sheer Adhesion Test** – Resist flow; Measurement of cohesive strength of an adhesive polymer

• **Peel Adhesion Test** – Resist removal; Force required to remove adhesive coating from the test substrate

• **Potency** – Drug content was found by dissolving a 0.64cm² patch for 2 hours and then the filtrate was analyzed using UV Spectrophotometry
Methods and Experiments

- **In-Vitro Drug Release Studies** – Evaluates the rate and extent of release of a drug substance from a transdermal patch

![Franz Cell Diagram](image)

Figure 15: Franz Cell – *in-Vitro* Dissolution Studies
Methods and Experiments

**In-Vitro Permeation** – In-vitro studies can help find the mechanism of skin permeation of the drug before it can be developed into a TDDS

**Factors Affecting In-Vitro Permeation:**
- Hydration time
- pH
- Transdermal Enhancers
- Temperature
- Thickness of skin
- Sampling intervals
Franz-diffusion cells were used in our studies, in which drug leaves an unstirred donor compartment, crosses through a membrane of thickness h and cross sectional area A, and accumulates in a stirred receiver compartment for which sink conditions were maintained. For this type of steady-state diffusion, we can use Fick’s First law,

\[ J = \frac{\text{d}M}{A \cdot \text{d}t} \]

Where, \( J \) = Flux (\( \mu \text{g cm}^{-2} \text{ hr}^{-1} \))
\( A \) = Cross sectional area of membrane (\( \text{cm}^2 \))
\( \frac{\text{d}M}{\text{d}t} \) = Amt of drug permeated vs. time (\( \mu \text{g/hr.} \))

From, experimental point of view, the flux can be calculated by below equation,

\[ J = \frac{\text{Slope}}{\text{Diffusion Area}} \]

Where, Slope = resultant slope of \( \frac{\text{d}M}{\text{d}t} \) vs. time

Diffusion area = \( A = 0.64 \text{ cm}^2 \)
Methods and Experiments

Shear Adhesion Test:

- Measurement of the cohesive strength of an adhesive polymer
- Influenced by weight and composition
- Shear adhesion determined by time it takes to pull patch off the plate

Fig 16: Force Tester
Peel Test from the Surface

- Force required to remove an adhesive coating from a test substrate
- Applied to steel plate
- Force required for patch to be removed is measured

Fig 17: Force Tester
Methods and Experiments

Peel Test from the Release Liner

- Liner is peeled from adhesive
- Peeled from panel at 180° at a specified rate
- Force required to peel from adhesive is measured

Fig 18: Force Tester
Methods and Experiments

Skin Permeation Study

- In-vitro skin permeation assay
- Samples were taken out every 2 hours
- Analyzed by UV Spectrophotometer at specified wavelength for drug content

Fig 19: Franz Diffusion Cell
Methods and Experiments

Cold Flow

\[
\text{ColdFlow}_{\text{norm}} = \frac{\text{Weight}_{\text{initial}} - \text{Weight}_{\text{final}}}{\text{Weight}_{\text{initial}} \times \text{Area}_{\text{TDDS}}}
\]

Fig 20: Cold Flow
## Results and Discussion

### Drug Solution

<table>
<thead>
<tr>
<th>Properties</th>
<th>SENS</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>-</td>
<td>9.5</td>
</tr>
<tr>
<td>Water Uptake</td>
<td>11.097%</td>
<td>-</td>
</tr>
<tr>
<td>Viscosity</td>
<td>77 cP</td>
<td>39 cP</td>
</tr>
<tr>
<td>Emulsification Rate</td>
<td>80 sec</td>
<td>-</td>
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Results and Discussion

Lidocaine formulation

<table>
<thead>
<tr>
<th>Properties</th>
<th>i-SENS</th>
<th>Control</th>
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<tbody>
<tr>
<td>pH</td>
<td>8.5</td>
<td>8.66</td>
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<tr>
<td>Water Content</td>
<td>6.34%</td>
<td>5.04%</td>
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<tr>
<td>Viscosity</td>
<td>447,505 cP</td>
<td>667,058 cP</td>
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Results and Discussion

Graph 1

Emulsion

Cumulative Conc

Times (hours)

Graph 1
Results and Discussion

Graph 2
Results and Discussion

Graph 3

Cumulative Concentration

- Emulsion
- Control
- Linear(Emulsion)
- Linear(Control)
## Results and Discussion

### Flux

<table>
<thead>
<tr>
<th></th>
<th>Emulsion</th>
<th>Control</th>
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<tr>
<td>Flux</td>
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<td>2.3</td>
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## Results and Discussion

### Physical Parameters

<table>
<thead>
<tr>
<th>Physical Parameters</th>
<th>Emulsion</th>
<th>Control</th>
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<tbody>
<tr>
<td>Weight of Patch</td>
<td>16.23 grams</td>
<td>16.19 grams</td>
</tr>
<tr>
<td>Weight of Liners</td>
<td>2.22 grams</td>
<td>2.21 grams</td>
</tr>
<tr>
<td>Weight of Adhesive</td>
<td>14.01 grams</td>
<td>13.98 grams</td>
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Results and Discussion

Shear Adhesion Test

**Emulsion**

<table>
<thead>
<tr>
<th>Load (N)</th>
<th>Time (Seconds)</th>
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</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
</tr>
<tr>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>0.6</td>
<td>25</td>
</tr>
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</table>

LP 1.35
RT Pass

**Control**

<table>
<thead>
<tr>
<th>Load (N)</th>
<th>Time (Seconds)</th>
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<tbody>
<tr>
<td>0.1</td>
<td>0</td>
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<tr>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>0.3</td>
<td>10</td>
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<tr>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>0.6</td>
<td>25</td>
</tr>
</tbody>
</table>

LP 0.85
RT Pass
Results and Discussion

Peel Test from Release Liner

Emulsion

Control

LP 0.00
RT Pass

LP -0.70
RT Pass
Results and Discussion

Peel Test from Surface

Emulsion

Control

LP 0.60
RT Pass

LP 0.10
RT Pass
Results and Discussion

Cold Flow = \frac{\text{Weight Initial} - \text{Weight Final}}{\text{Weight Initial} \times \text{Area TDDS}}

<table>
<thead>
<tr>
<th>Emulsion</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>0.000792 g/cm²</td>
<td>0.000591 g/cm²</td>
</tr>
</tbody>
</table>
CONCLUSION

- **i-SENS TDS** are promising and innovative drug delivery systems that can be tailored to achieve desired drug release profile *in-vivo*.
- **i-SENS TDS** can be considered as an alternative topical drug delivery systems to address the problems such as low drug load, irritation, and stability are associated with traditional/conventional topical drug delivery systems gels, SENS lotions, and TDS.
- **i-SENS TDS** is an ideal to deliver hydrophilic and lipophilic molecules.
Thank you!

Any Questions
Please Email: R&D Department
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gsridhar@ascentpharm.com