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

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OBJECTIVE

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

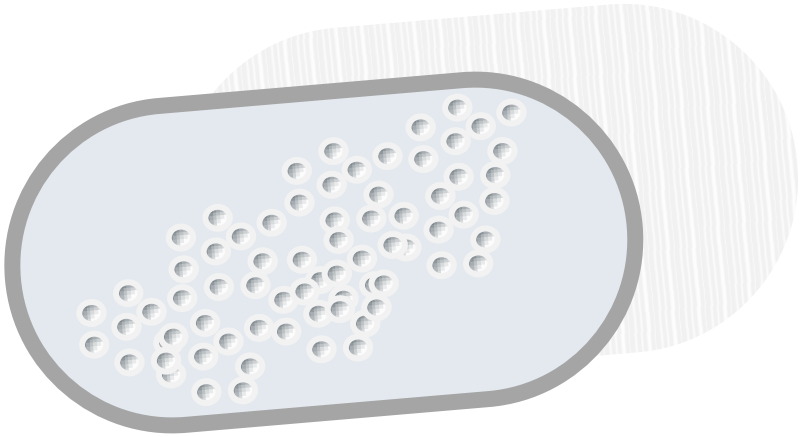


Fig 1: ***i-SENS Transdermal System***

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

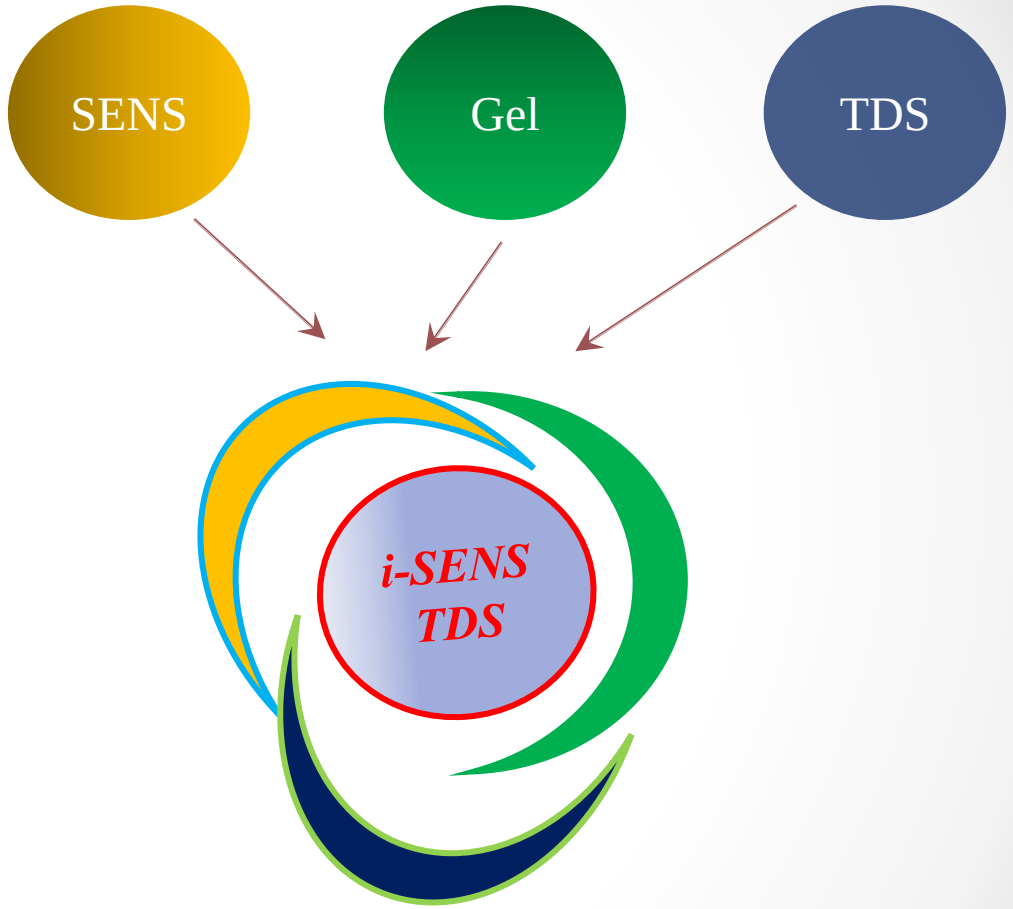


Figure 2: Conceptual Diagram of *i-SENS TDS*

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

Technology Extension

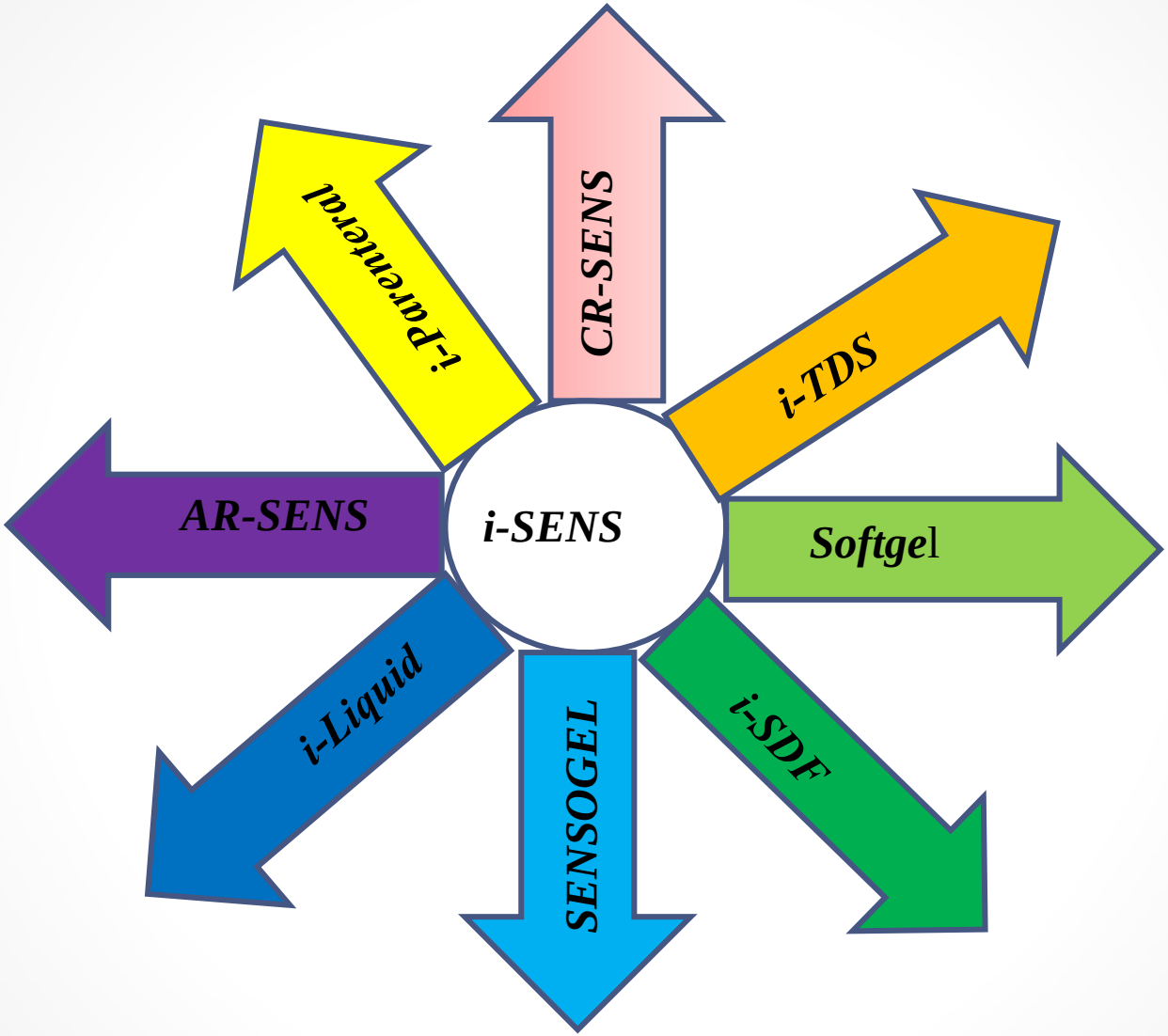


Fig 3: Technology Extension

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

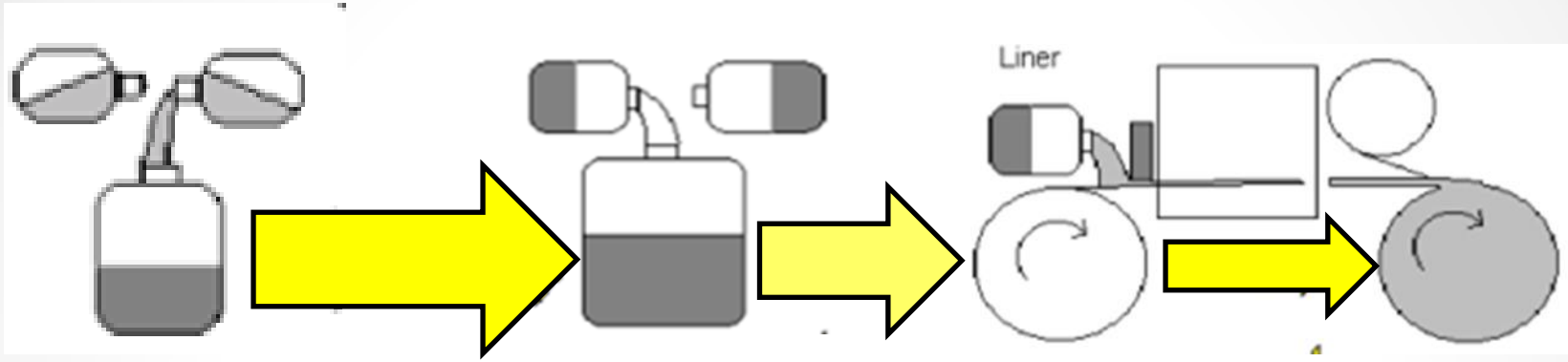
Lidocaine:

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

Physiochemical Properties of Lidocaine

Attributes	Observations
Molecular Formula	$C_{14}H_{22}N_2O$
Molecular Weight	234.33728 g/mol
Color	White or Slightly Yellow, crystalline powder
Boiling Point	159-160 °C at 2.00E+00 mm Hg
Melting Point	68 °C
Solubility	Very soluble in alcohol, chloroform; freely soluble in ether, benzene and dissolves in oils
pKa	8.01

Methods and Experiments



SENS Preparation **_i-SENS_ TDS BASE Preparation** **_i-SENS_ Coating on Felt**

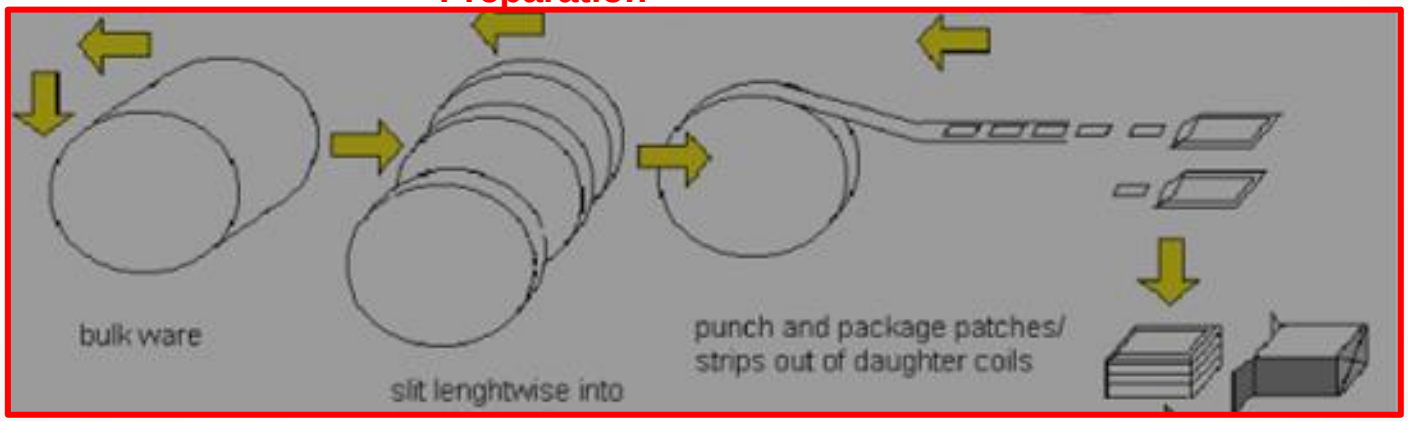


Fig 5: Flow diagram showing the steps of Manufacturing

Introduction

Phase Diagram

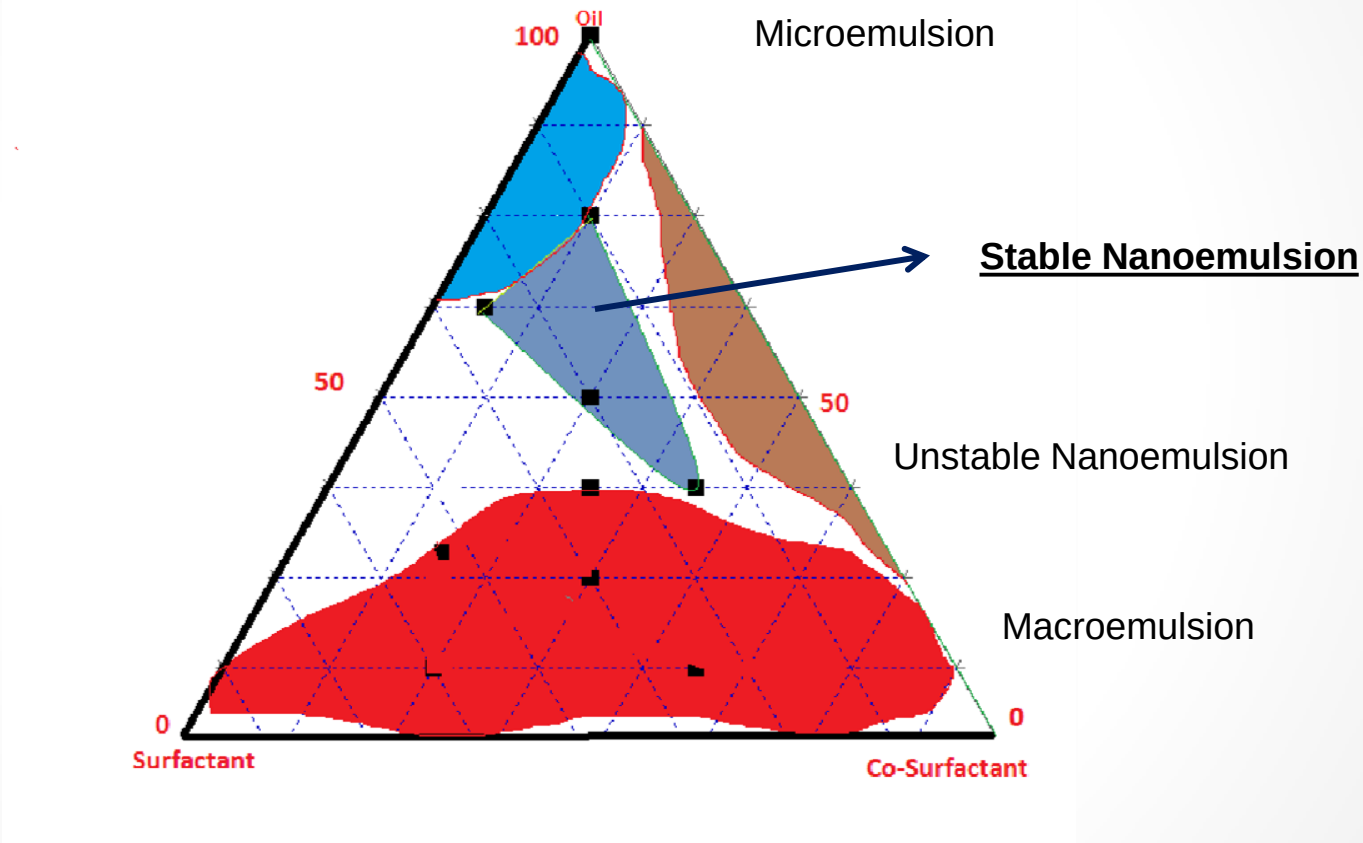


Fig 6: Phase Diagram

Methods and Experiments

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.

S.No	Ingredient	Functionality
1	Lidocaine	API
2	1, 3 butanediol	Solubilizer
3	Cremophore EL	Surfactant
4	Capmol MCM	Solubilizer

Methods and Experiments

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.

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

Methods and Experiments

Fig 7: Coating Machine

Methods and Experiments

Fig 8: Harro Hofliger Packaging Machine

Methods and Experiments

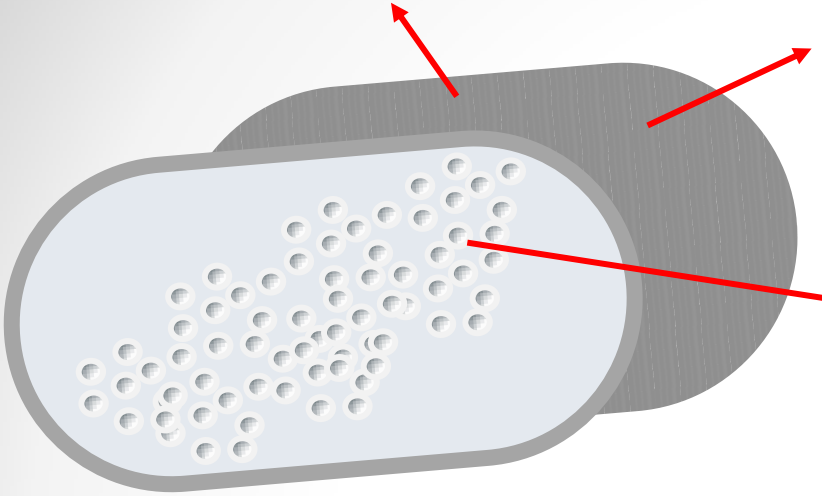


Fig 9: *i-SENS Transdermal Patch*:

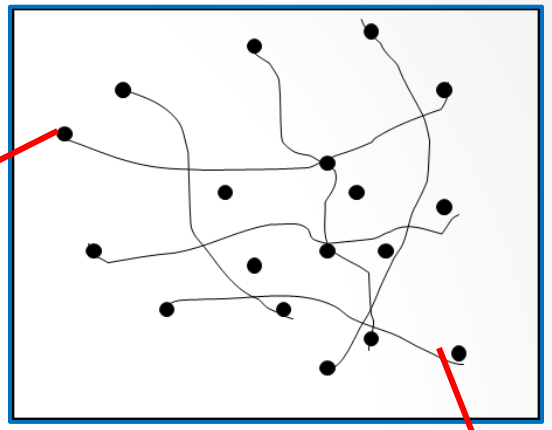


Fig 10: Physically Bonded SENS Network in Polymer

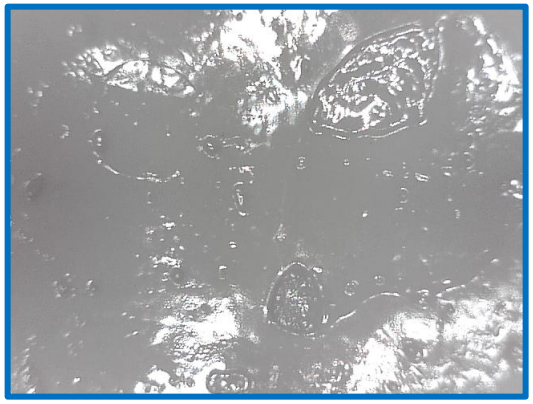
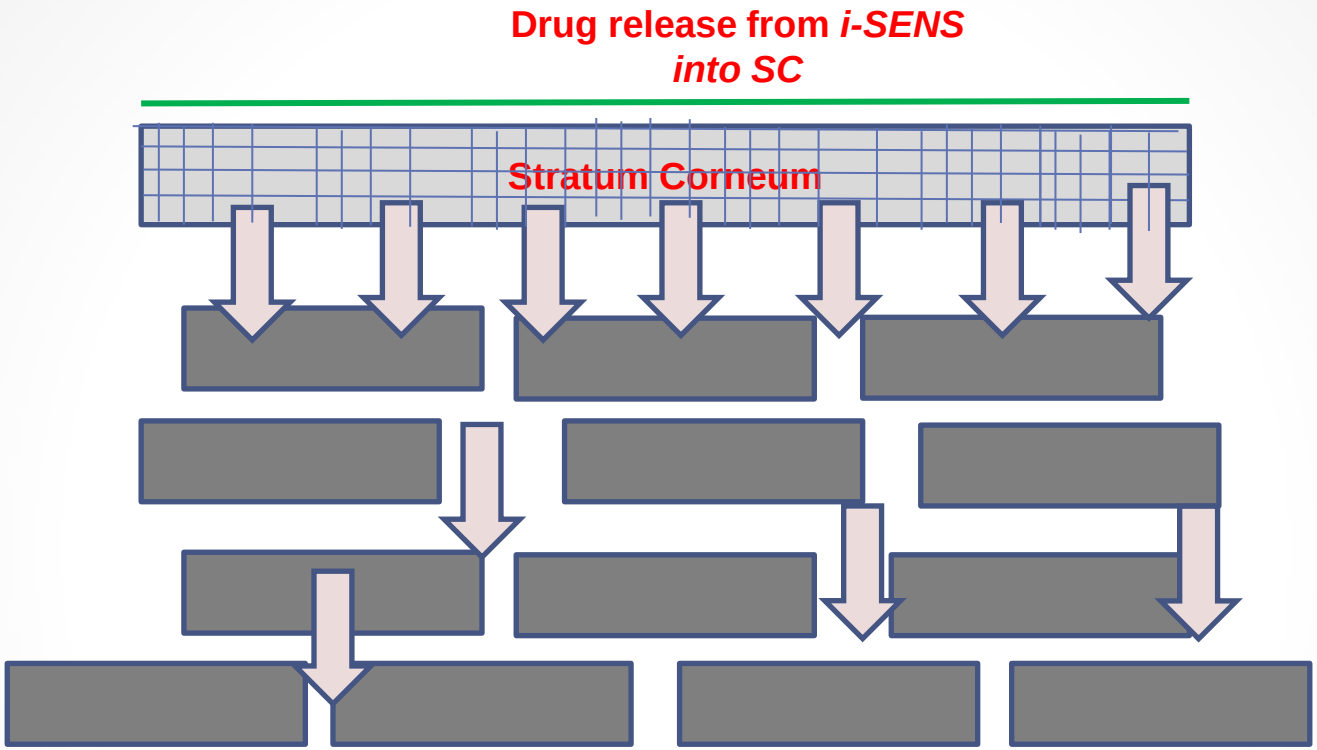


Fig 11: Microphotograph of i-SENS Transdermal Patch Gel

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

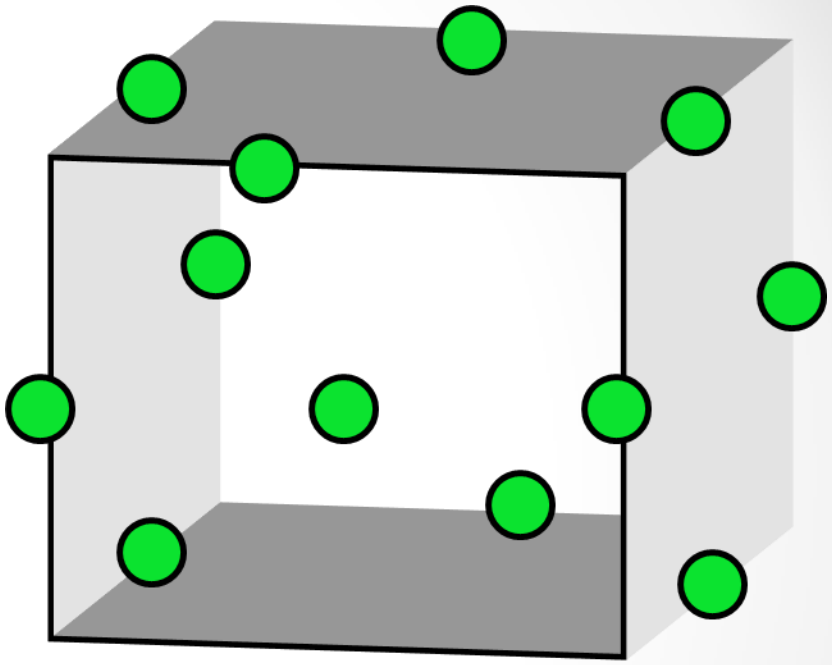


Figure 14 : Box-Optimization DoE for investigating the effect of formulation variables

- **Drug Release**
- **Moisture Level**
- **Viscosity**
- **Peel Strength**

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 0.64cm^2 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

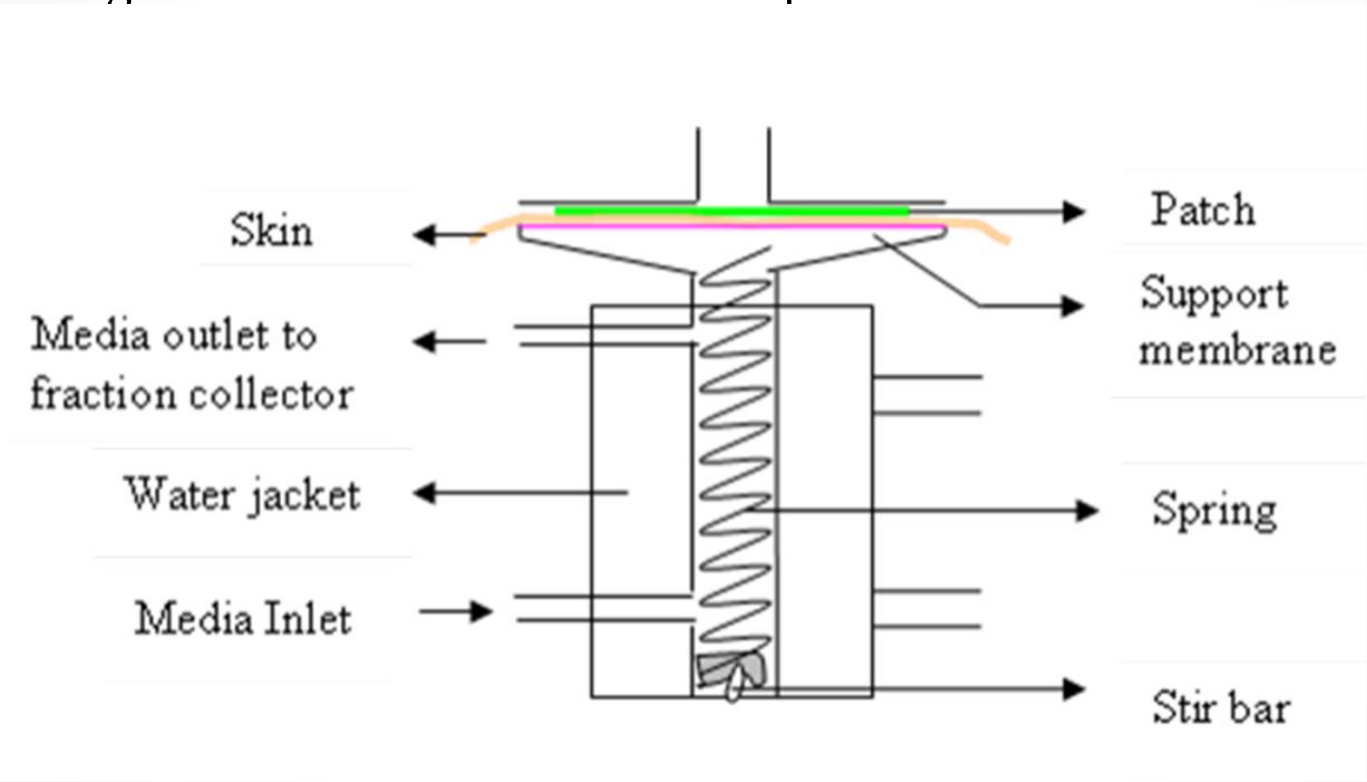


Figure 15: Franz Cell – *in-Vitro* Dissolution Studies

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

Methods and Experiments

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,

$$J = \frac{dM}{A*dt}$$

Where, J = Flux (µg cm^{-2} hr^{-1})
A = Cross sectional area of membrane (cm^2)
$\frac{dM}{dt}$ = Amt of drug permeated vs. time (µg/hr.)

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

$$J = \frac{Slope}{Diffusion\ Area}$$

Where, Slope = resultant slope of $\frac{dM}{dt}$ vs. time

Diffusion area = A = 0.64 cm^2

Methods and Experiments

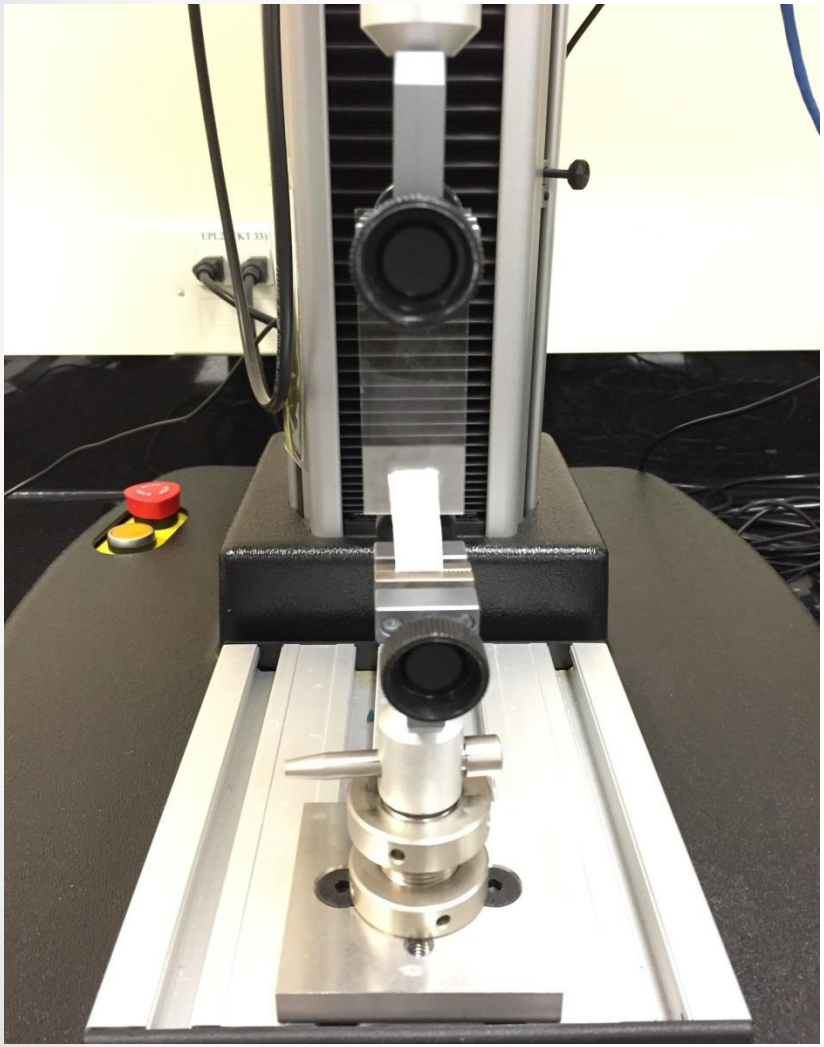


Fig 16: Force Tester

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

Methods and Experiments

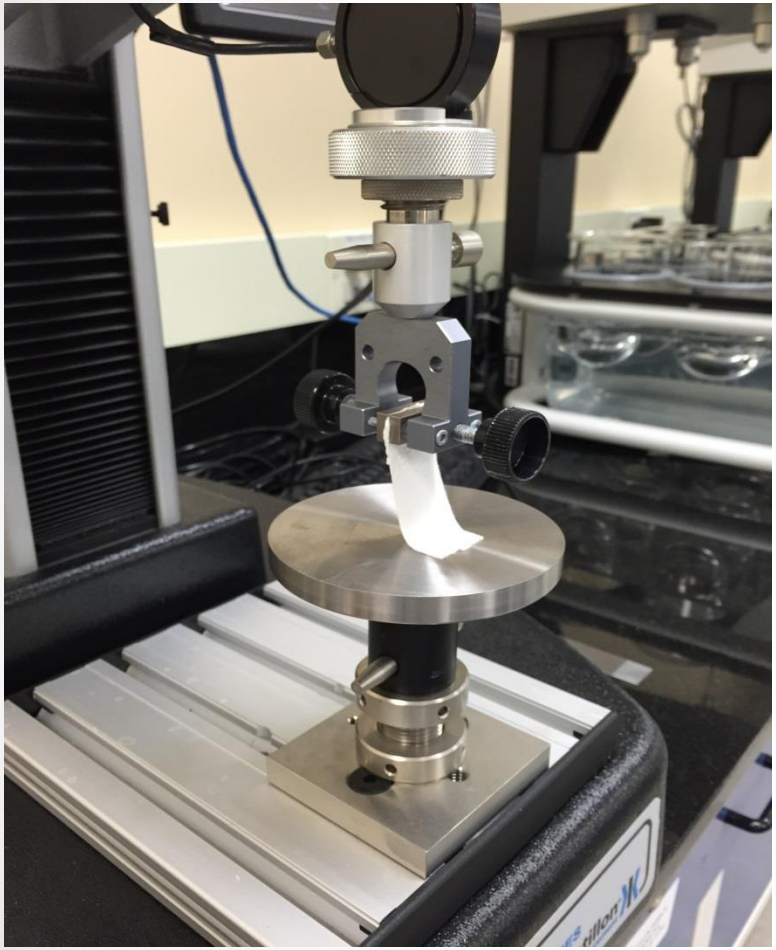


Fig 17: Force Tester

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

Methods and Experiments

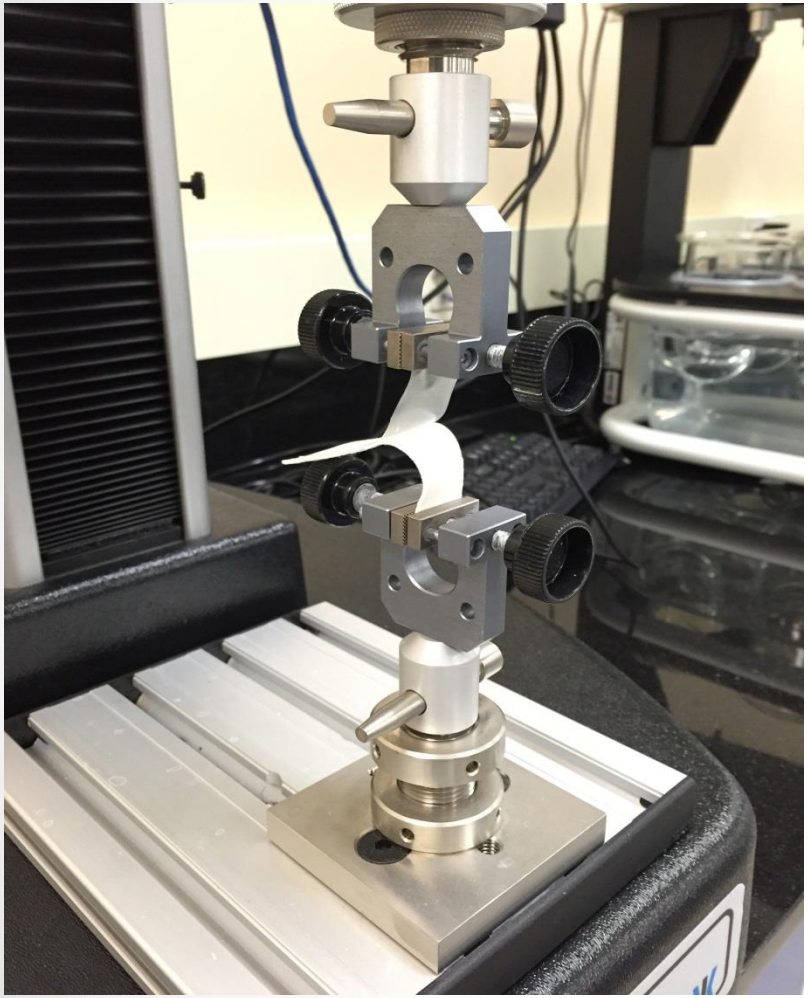


Fig 18: Force Tester

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

Methods and Experiments

Fig 19: Franz Diffusion Cell

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

Methods and Experiments

Cold Flow

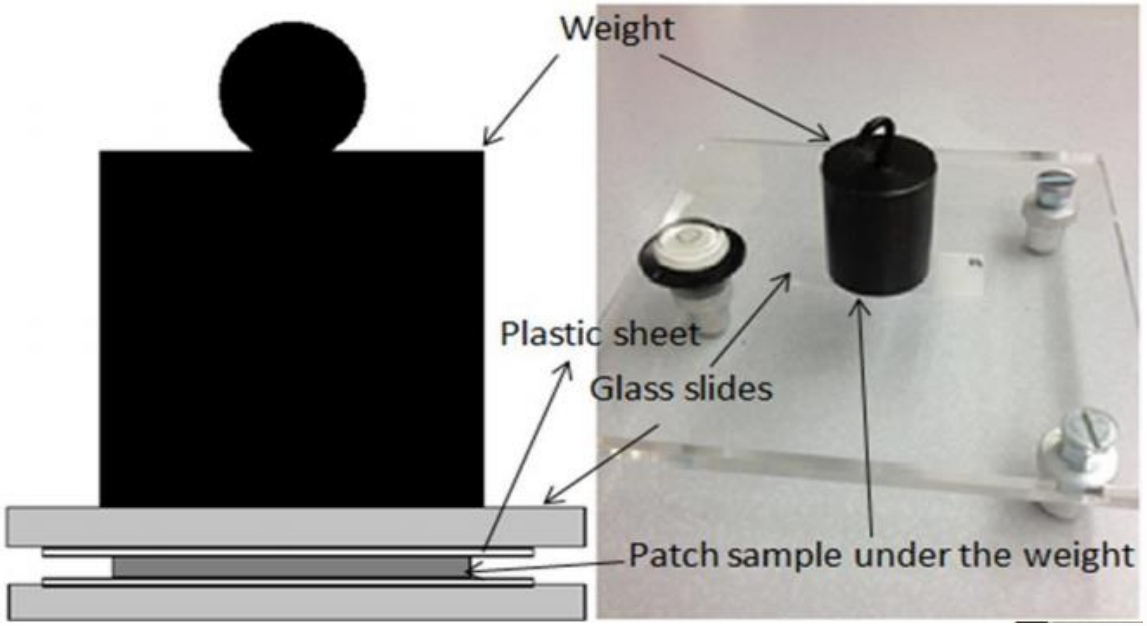


Fig 20: Cold Flow

$$ColdFlow_{norm} = \frac{Weight_{initial} - Weight_{final}}{Weight_{initial} \times Area_{TDDS}}$$

Results and Discussion

Drug Solution

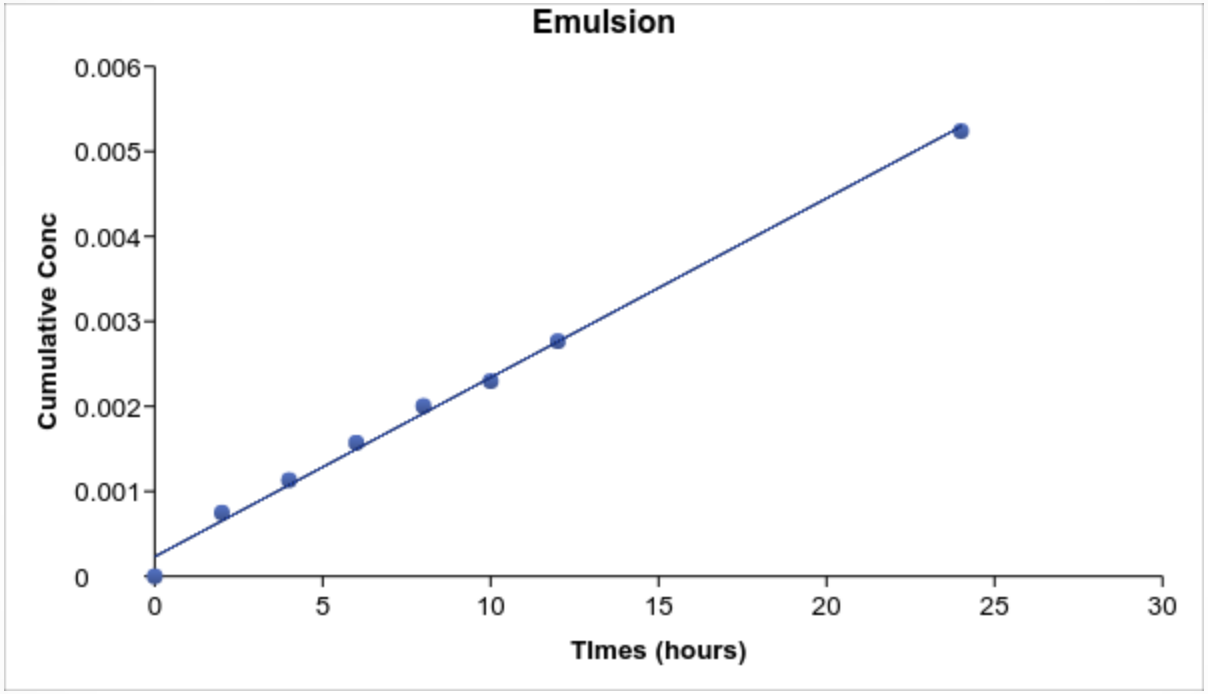
Properties	*SENS*	Control
pH	-	9.5
Water Uptake	11.097%	-
Viscosity	77 cP	39 cP
Emulsification Rate	80 sec	-

Results and Discussion

Lidocaine formulation

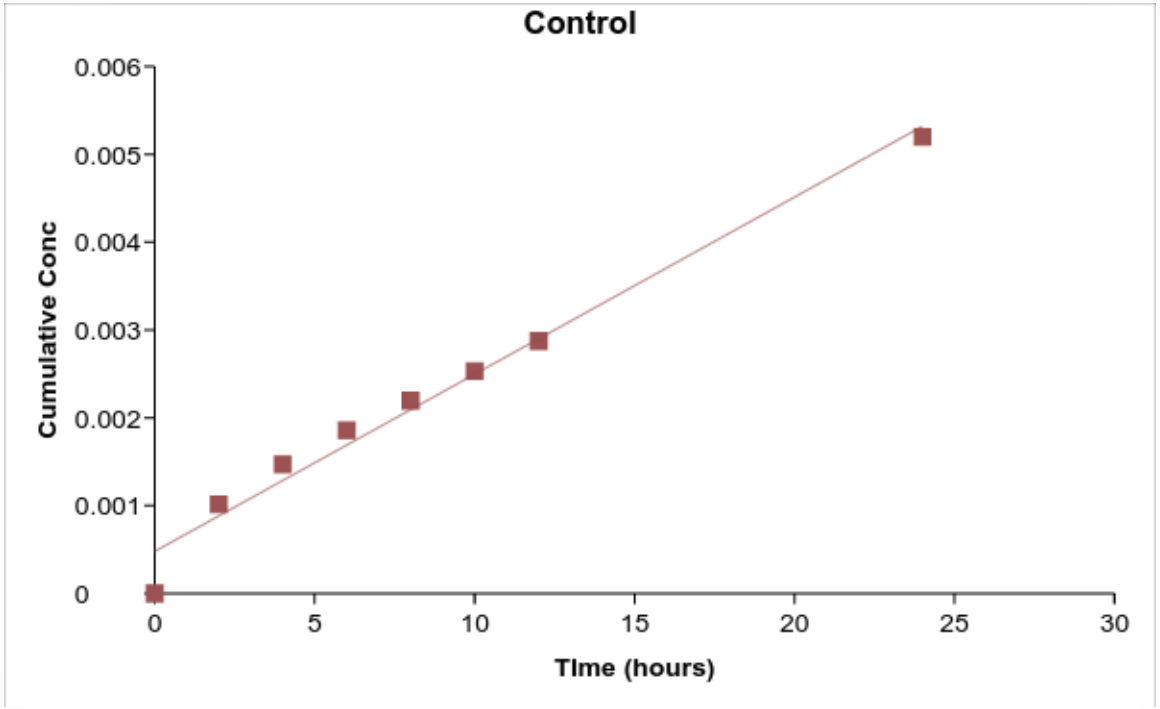
Properties	*i-SENS*	Control
pH	8.5	8.66
Water Content	6.34%	5.04%
Viscosity	447,505 cP	667,058 cP

Results and Discussion



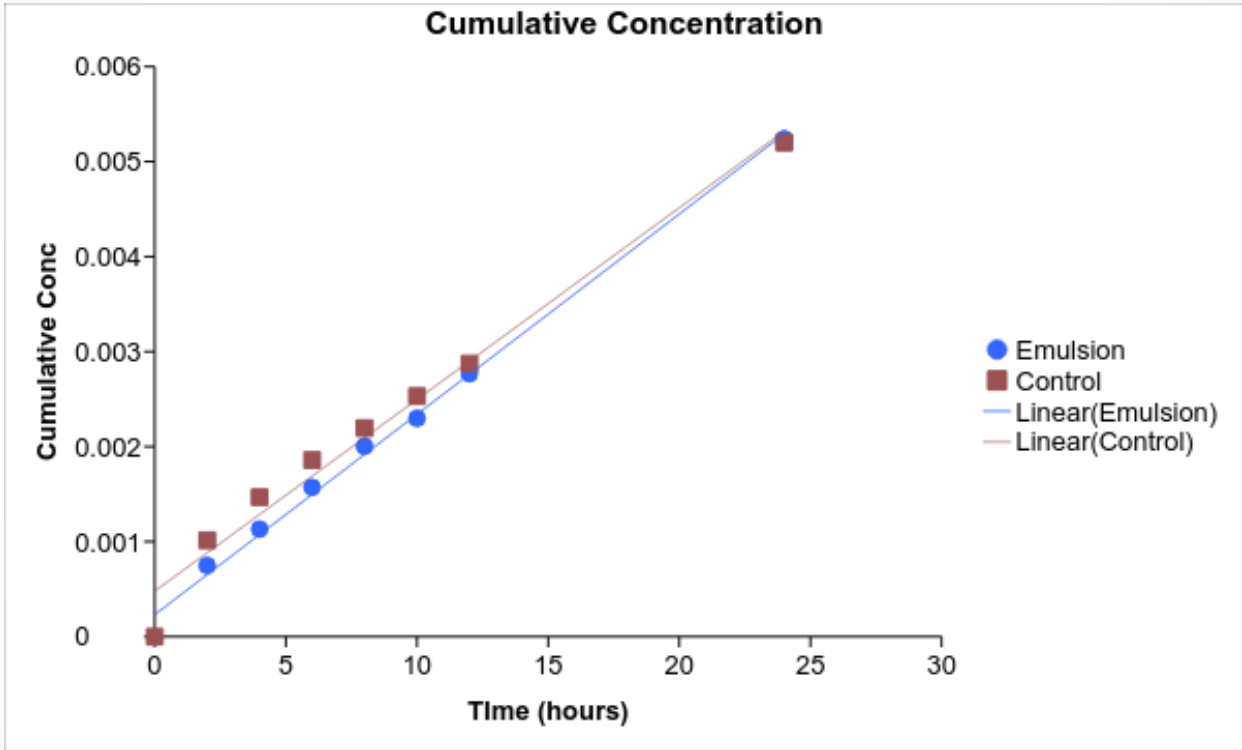
Graph 1

Results and Discussion



Graph 2

Results and Discussion



Graph 3

Results and Discussion

Flux

	Emulsion	Control
Flux	2.2	2.3

Results and Discussion

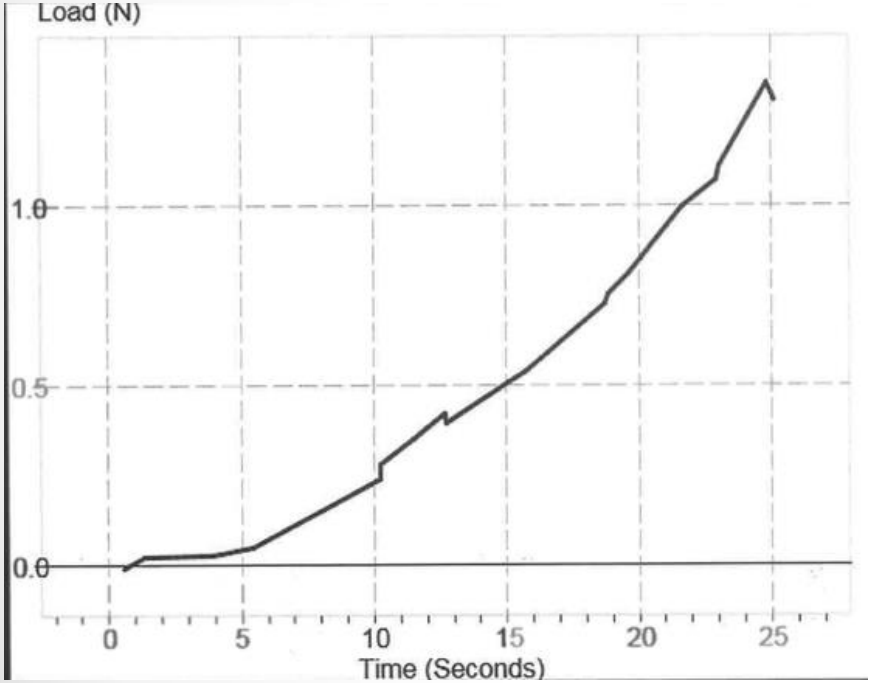
Physical Parameters

Physical Parameters	Emulsion	Control
Weight of Patch	16.23 grams	16.19 grams
Weight of Liners	2.22 grams	2.21 grams
Weight of Adhesive	14.01 grams	13.98 grams

Results and Discussion

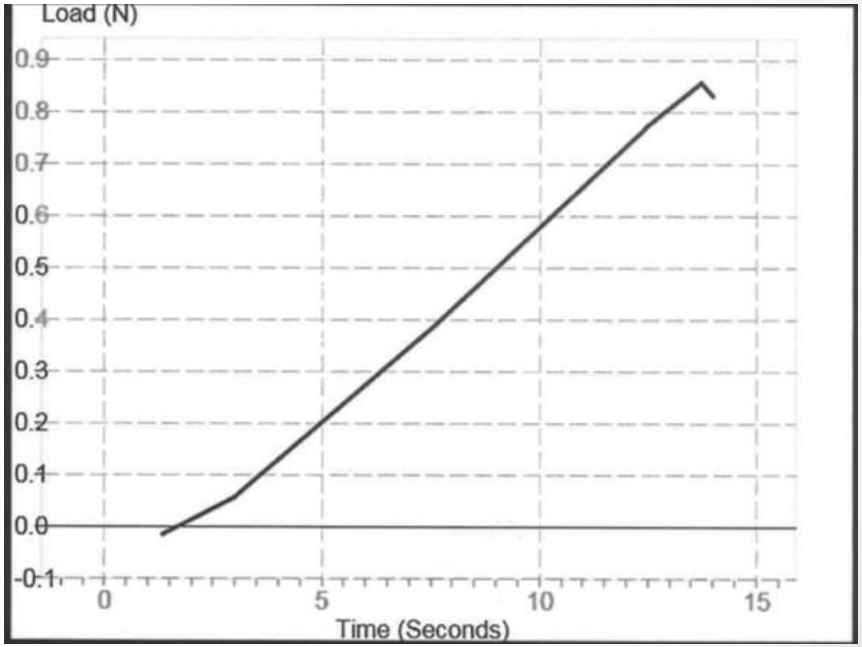
Shear Adhesion Test

Emulsion



LP 1.35
RT Pass

Control

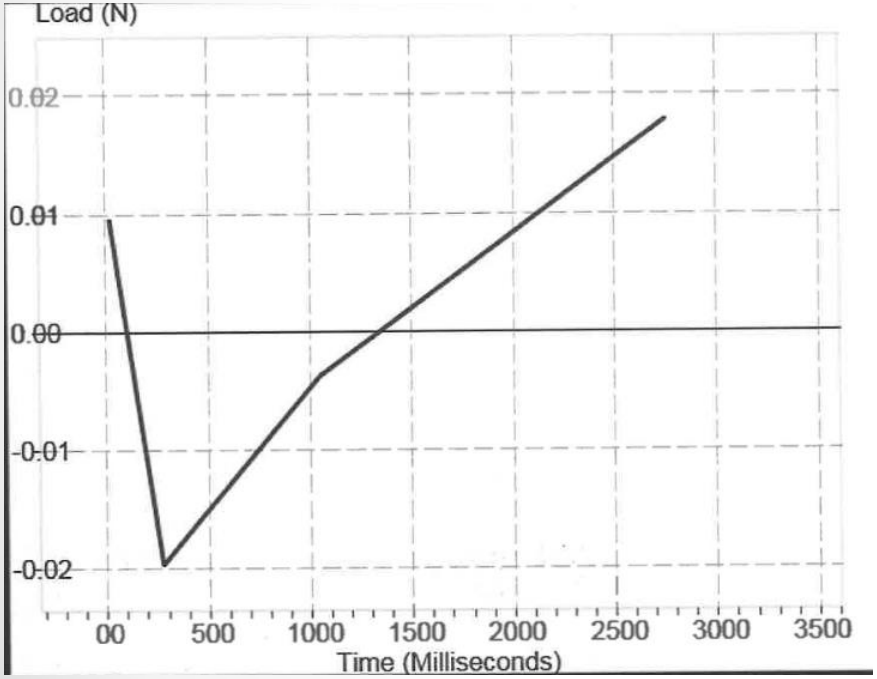


LP 0.85
RT Pass

Results and Discussion

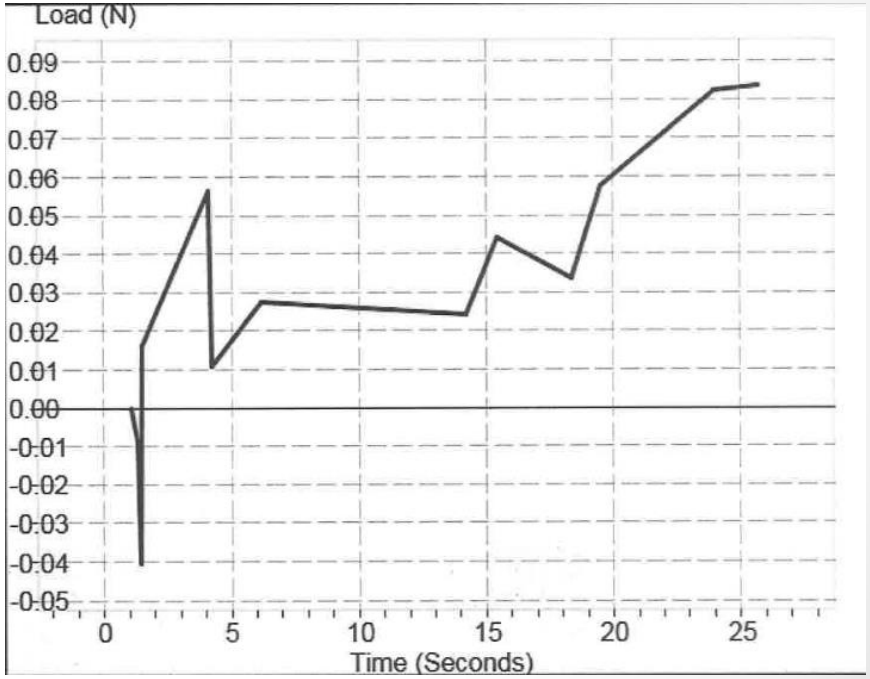
Peel Test from Release Liner

Emulsion



LP 0.00
RT Pass

Control

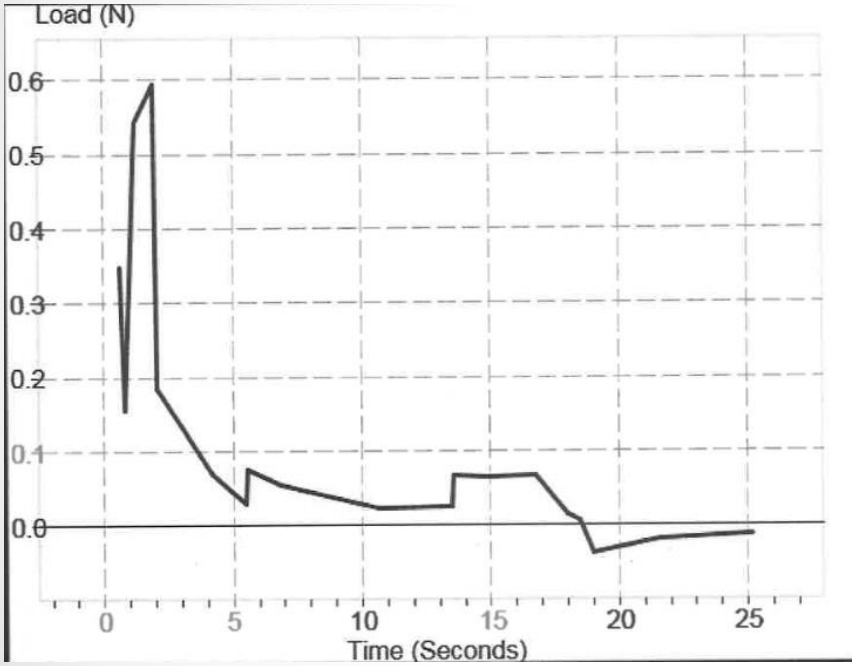


LP -0.70
RT Pass

Results and Discussion

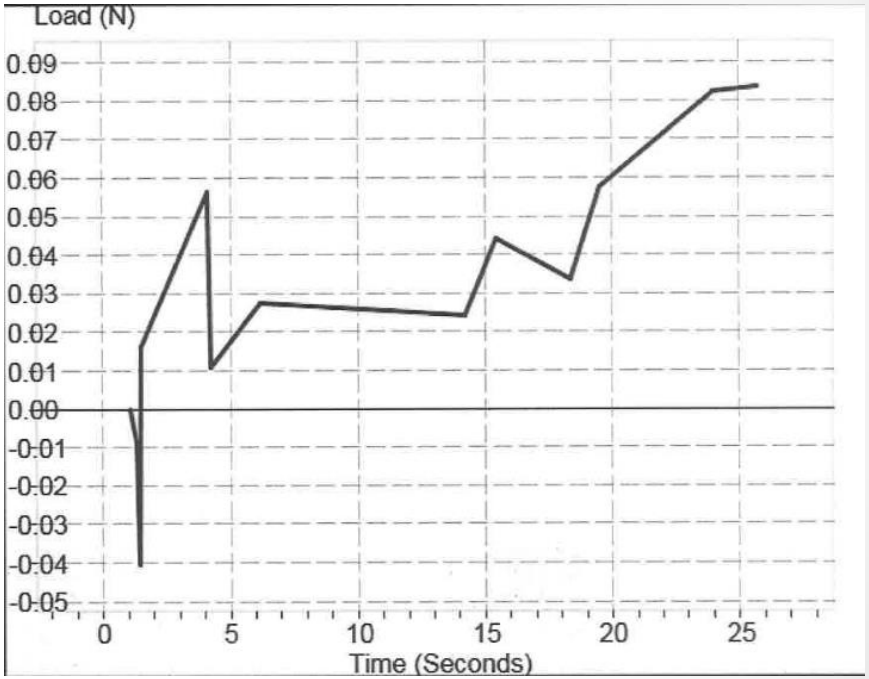
Peel Test from Surface

Emulsion



LP 0.60
RT Pass

Control



LP 0.10
RT Pass

Results and Discussion

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

Emulsion	Control
0.000792 g/cm^2	0.000591 g/cm^2

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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