Gel-based high-permeation vesicles for localized fulvestrant delivery to treat breast cancer

Presenter: **Junia Akhtar**, Ph.D. Scholar
NIPER, S.A.S. Nagar, India
Mail: juniaakhtar8@gmail.com

Supervisor: Dr. Sanyog Jain
Prof. and HOD, Department of Pharmaceutics,
NIPER, S.A.S. Nagar, India

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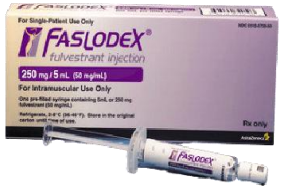
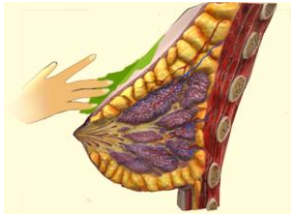
NEXT-GENERATION DELIVERY INNOVATIONS

Introduction



Marketed fulvestrant *i.m.* injection

To overcome these problems



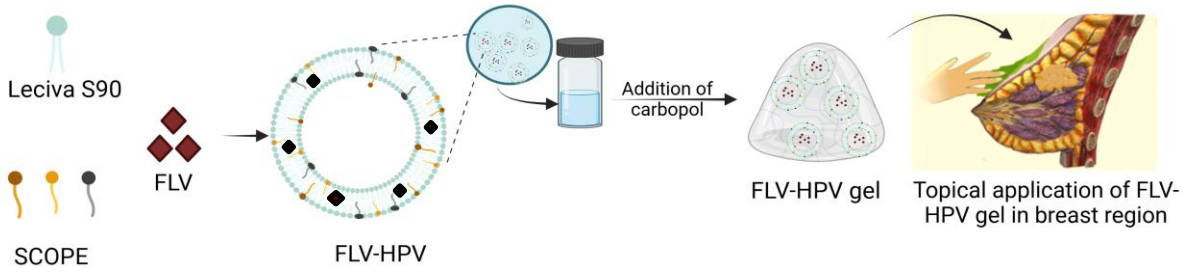
Localized delivery of Fulvestrant (FLV) in breast region

Barriers in Transdermal delivery

- Skin structure and its physiological properties
- Poor physicochemical properties of drug
- Biocompatibility issues

Problems associated

- Gastrointestinal disturbances: nausea, vomiting, constipation, diarrhea
- Hot flushes
- Systemic side effects



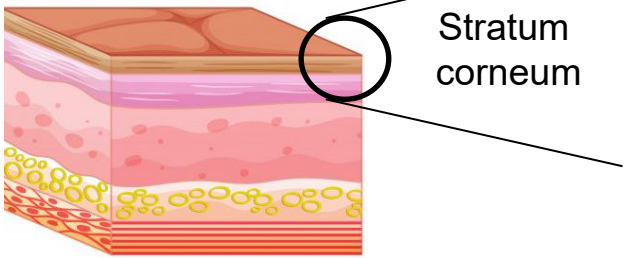
Rationale

CARRIER BASED

- HPVs are ultra deformable vesicles
- Deep penetration potential attributed to its composition
- High molecular weight and solubility issues can be overcome by the use of HPV

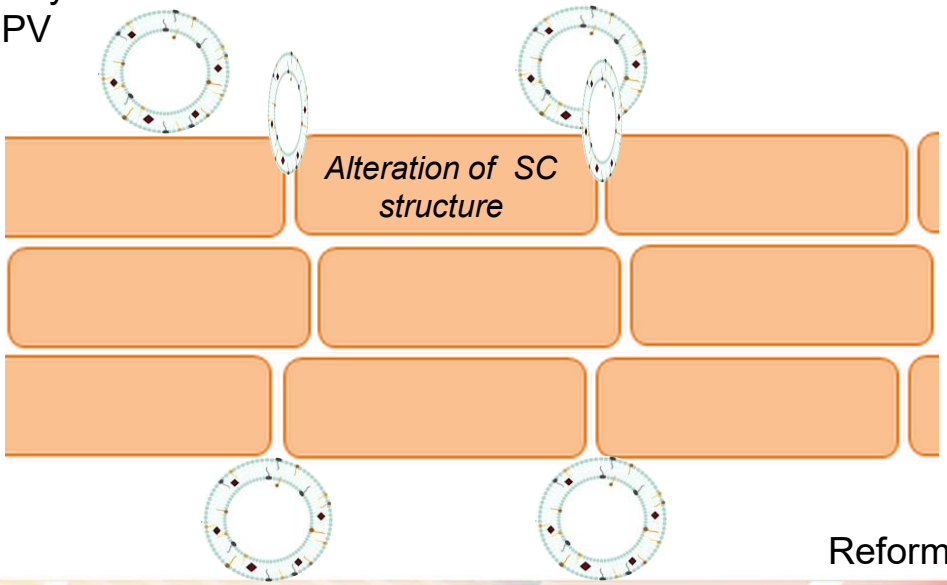
DRUG DELIVERY APPROACH BASED

- LDD approach has been used
- It tends to maximize the concentration of drug in breast tissue and minimizes systemic toxicity



Stratum corneum

Skin layers



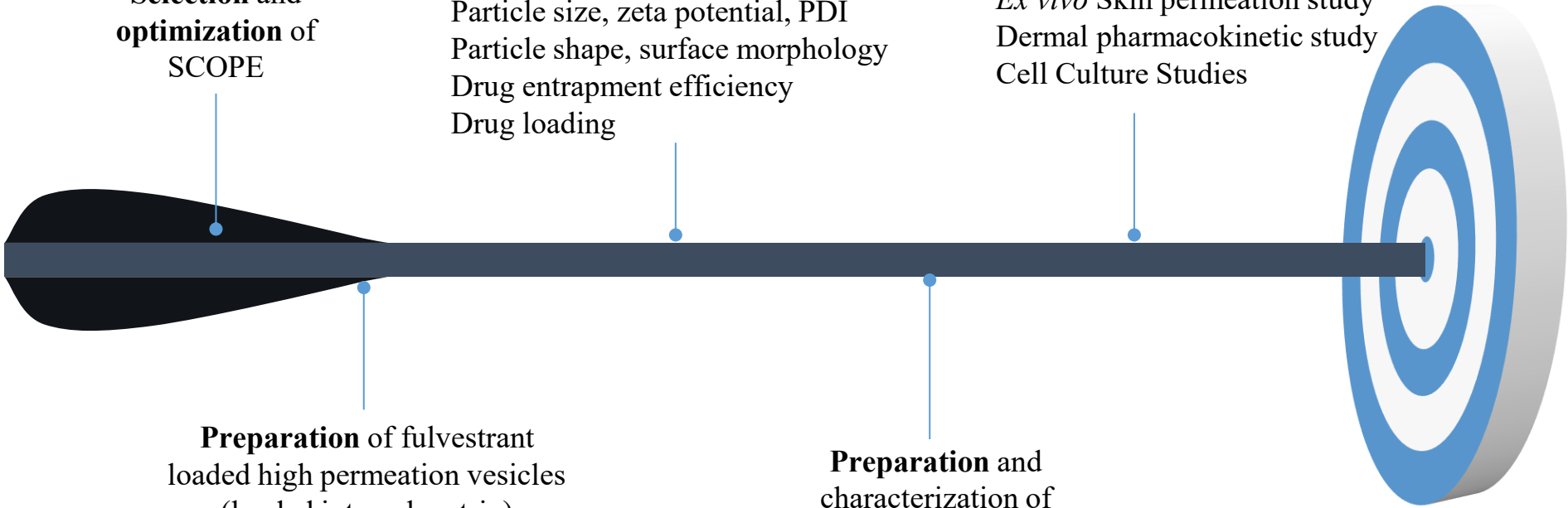
Enhanced penetration and permeation

Objectives

Selection and **optimization** of SCOPE

Characterization of developed formulation
- Particle size, zeta potential, PDI
- Particle shape, surface morphology
- Drug entrapment efficiency
- Drug loading

***In vitro* studies**
- Release study
- *Ex vivo* Skin permeation study
- Dermal pharmacokinetic study
- Cell Culture Studies

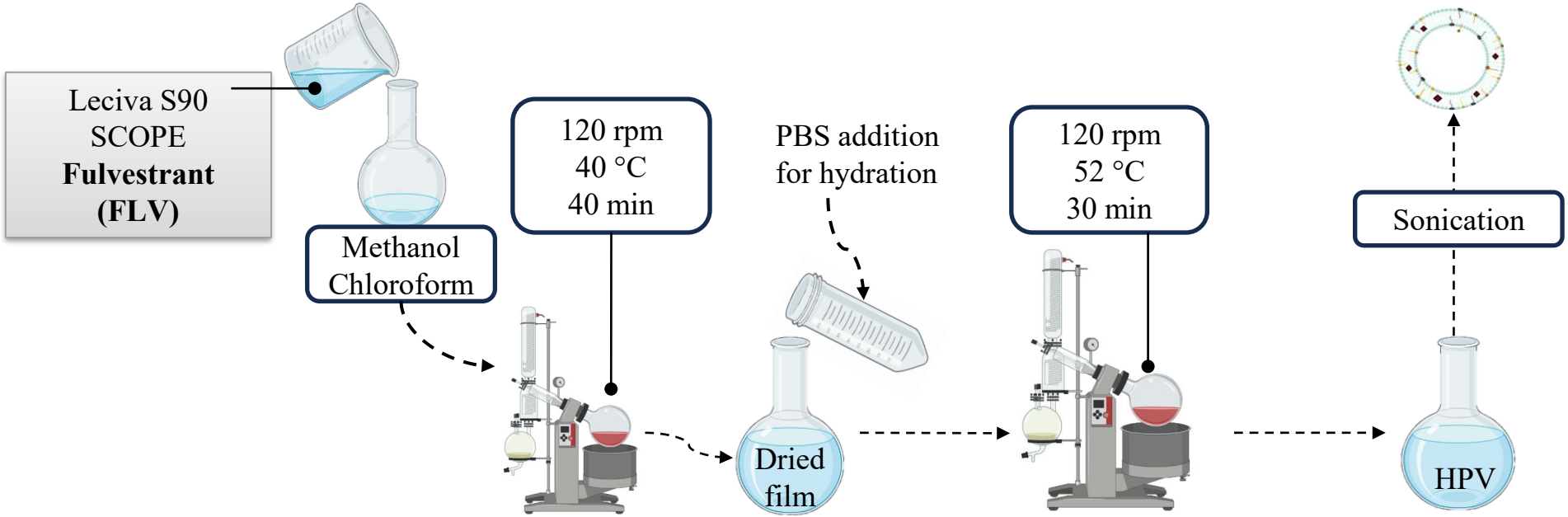


Preparation of fulvestrant loaded high permeation vesicles (loaded into gel matrix)

Preparation and characterization of HPVs loaded gel

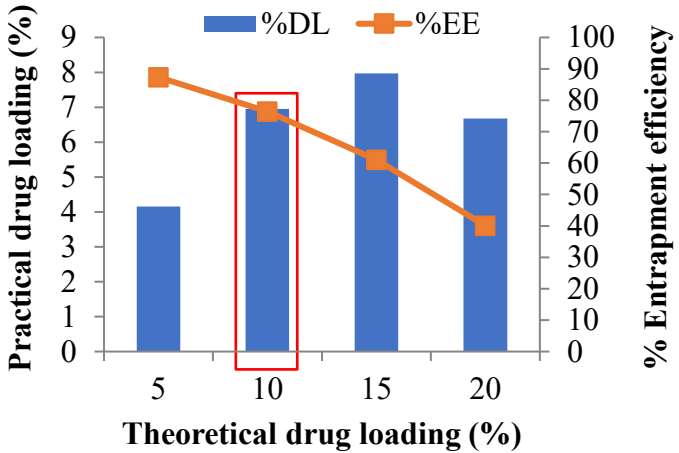
Method

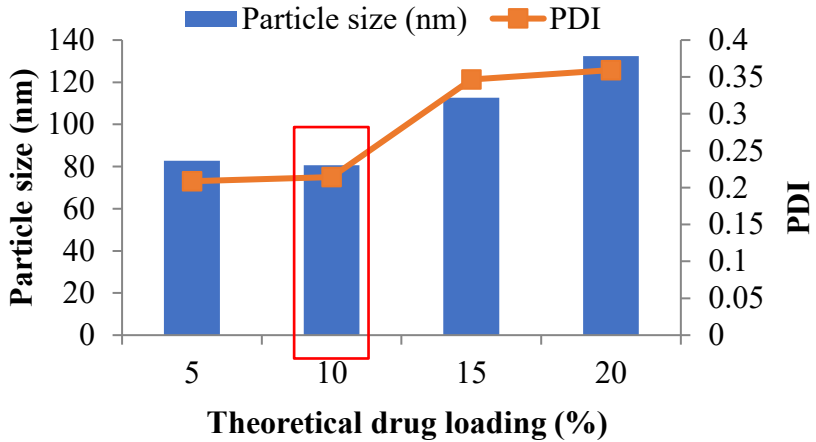
Fulvestrant-loaded HPV fabrication process by Thin Layer Hydration Method



Results

Optimization of Drug loading and Entrapment Efficiency

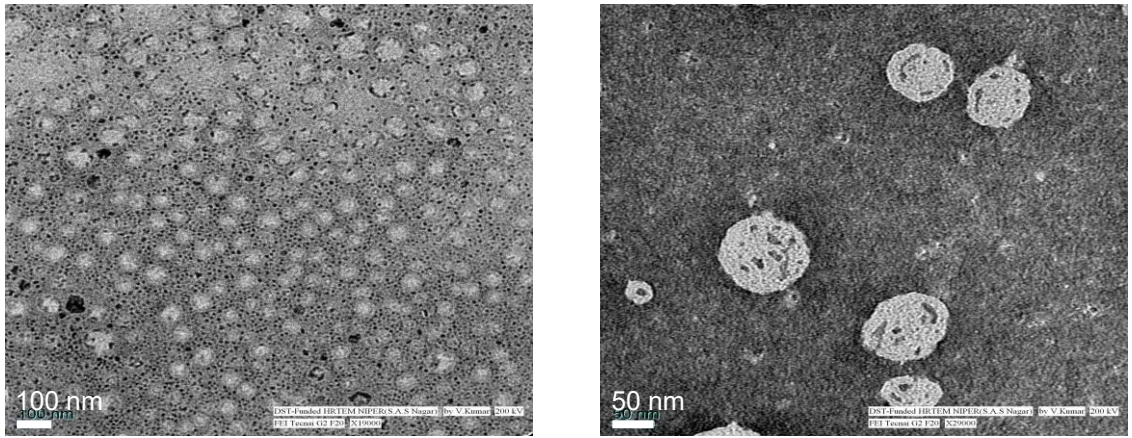




Theoretical Drug Loading (%)	Amount of drug added (mg)	Entrapment efficiency (%)	Practical Drug Loading (%)	Size (nm)	PDI
5	0.75	87.35±2.23	4.16±0.11	82.66±2.01	0.209±0.007
10	**1.5**	**76.45±3.54**	**6.95±0.32**	**80.64±2.32**	**0.214±0.01**
15	2.25	61.08±6.11	7.967±0.79	112.63±7.59	0.345±0.05
20	3	40.07±10.48	6.68±1.76	132.37±6.29	0.36±0.012

Characterization of HPV

Vesicle Size (nm)	PDI	% EE	% Drug Loading
83.89 ± 1.22	0.295 ± 0.027	85.79 ± 0.372	8.58 ± 0.016



TEM images of FLV-loaded HPVs

Preparation of HPV-loaded gel

- The prepared HPVs formulation was loaded in **Carbopol Gel (934P)**
- Using **Overhead Stirrer**
- Concentration optimized: **1.5% w/v**

A weighed amount of Carbopol powder was hydrated

Formulation was added and allowed to stir on overhead stirrer

HPVs loaded gel

Characterization of HPV-loaded gel

Visual observation: Translucent, non-gritty, no phase separation

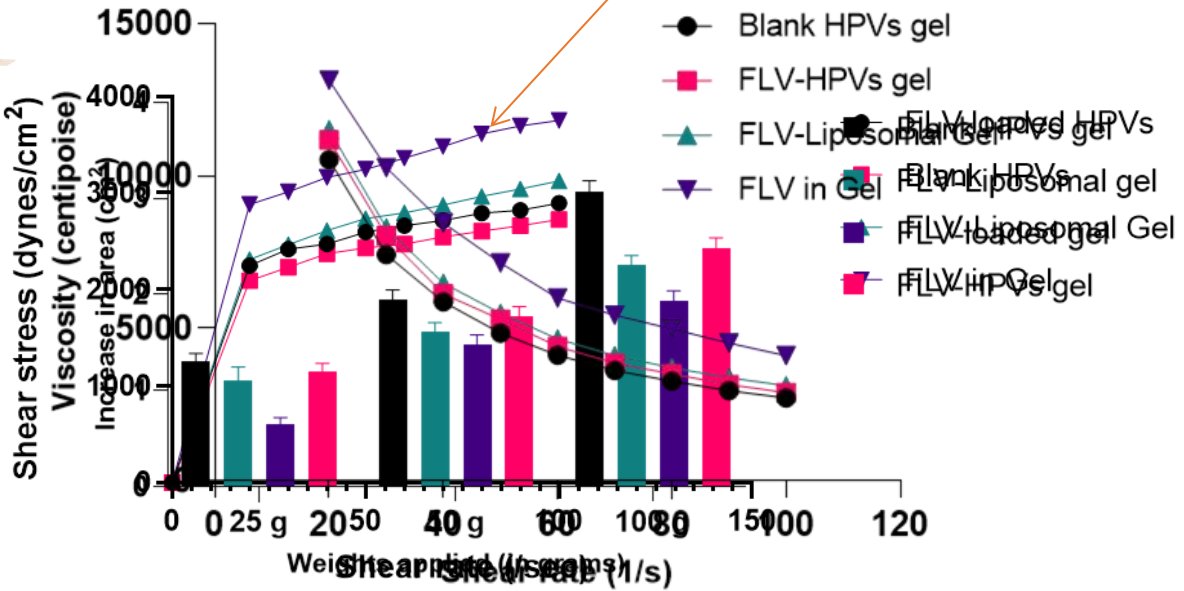
pH: Neutral to slightly acidic

Rheological Behavior

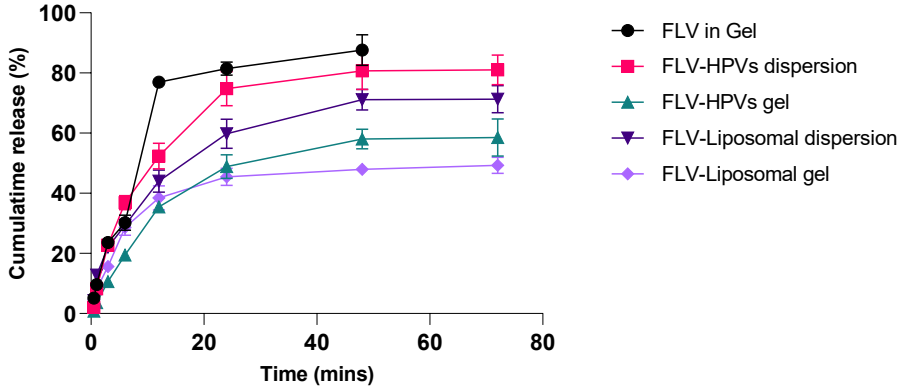
Spreadability

Viscosity

Pseudoplastic behavior



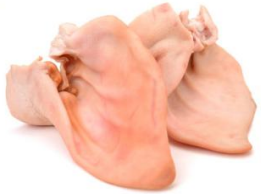
In-vitro Release Study



Formulation	R^2 values				n value
	Zero order	First order	Higuchi	Korsmeyer Peppas	Korsmeyer Peppas model (n)
Liposomes	0.855	0.654	0.971	0.965	0.35
HPVs	0.872	0.725	0.995	0.932	0.39
HPVs gel	0.894	0.64	0.978	0.945	0.33

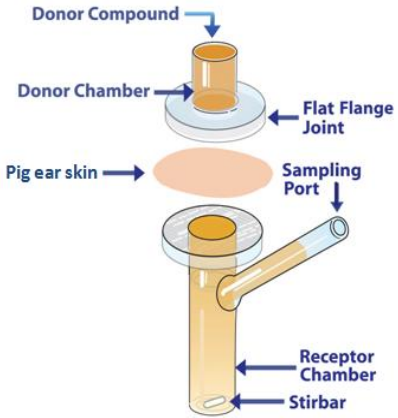
R. Swami *et al.*, Int J Pharm 486 (2015) 287-296

Ex-vivo Study



Pig ear skin

Cut in equal sq. pieces

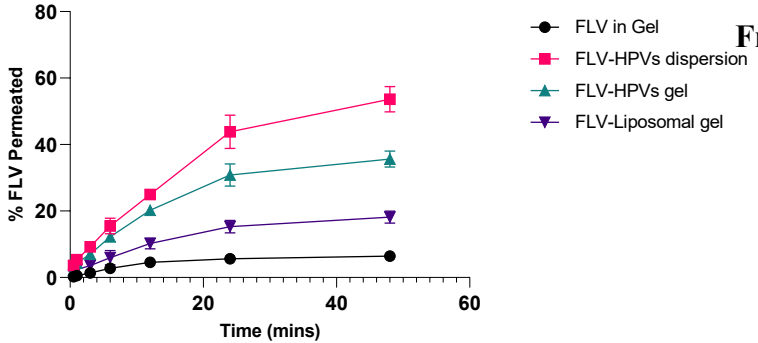


Franz diffusion cell

Aliquots withdrawn at specific time intervals and analysed by HPLC

Cell placed in the stirrer at specific rpm and temp. for 48 hours

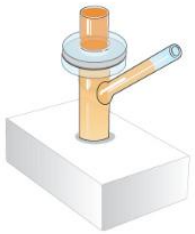
Skin permeation study



- Permeation of free drug and different formulations is compared
- Permeation order:

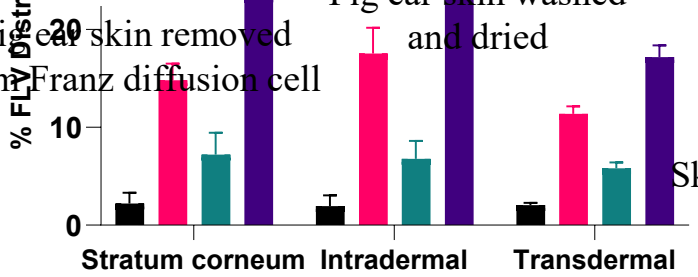
HPVs formulation > HPVs gel > Liposomal formulation > Free drug

Dermal distribution study

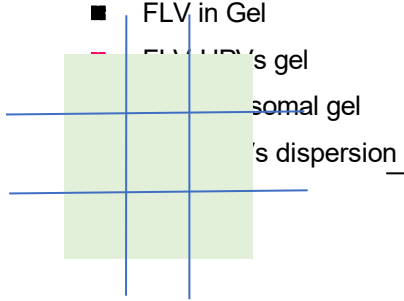


Pig ear skin removed from Franz diffusion cell

Pig ear skin washed and dried



Tape stripping to remove stratum corneum



Skin section cut into pieces

Tape digested to extract drug present in **SC**

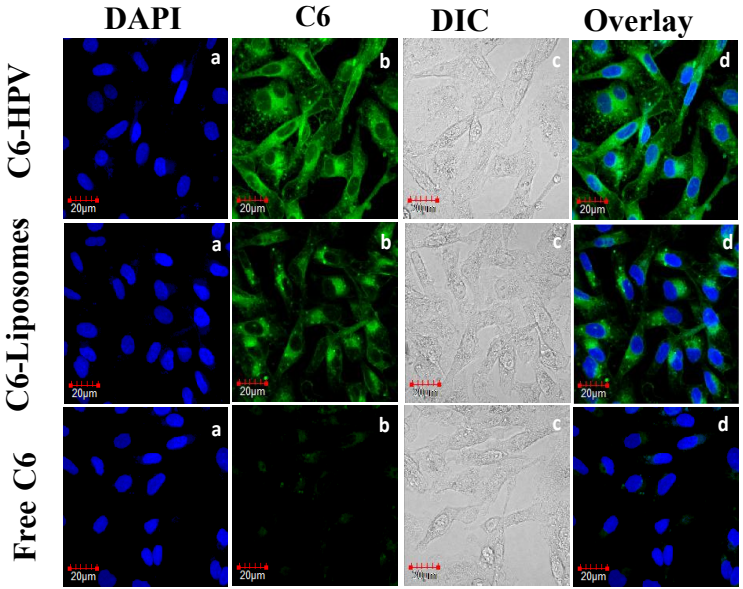
Total % drug distribution

- Free drug ~ 5%
- Liposomal gel ~ 19%
- HPVs gel ~ 44%
- HPVs ~ 67%

Samples analyzed for drug content

Cellular uptake study

MDA-MB-231 cells upon incubation for 3 h



Uptake in MDA-MB-231 cell lines

C6-HPVs> C6-Liposomes> Free C-6

Cytotoxicity study

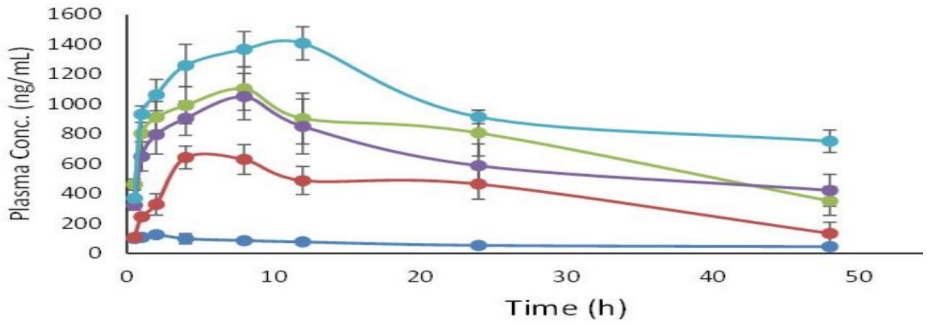
➢ Cell cytotoxicity of free drug and drug-loaded formulations was carried out and determined using **MTT assay**

Inference

Concentration-dependent reduction in percentage cell viability could be observed

Formulation	IC_{50} values (μM)
Free FLV	98.23±1.25
FLV Liposomes	0.18±1.07
FLV HPVs	0.37±0.95

Pharmacokinetic study



Inference

The HPV treated animals showcased ~16 folds increment in AUC and ~ 4 folds increment in $t_{1/2}$ values as compared to free drug in gel indicating the effectiveness of HPVs in improving skin permeation

Parameters	FLV in gel	SCOPE in gel	FLV Liposomal gel	FLV HPV gel	FLV HPV solutions
C_{max} (ng/ml)	125.89±53.2	642.4±132.04	1303.4±64.33	1406.6±201.96	1049.4±201.9
AUC (ng/ml h)	3015.9±159.4	18976.6±423.55	35420.3±552.1	48335.3±723.6	31089.8±636.5
$T_{1/2}$ (h)	12.8±2.1	18.5±1.63	25.1±2.41	42.7±14.30	31.9±2.358
MRT (h)	16.8±1.05	18.6±3.4	19.4 ±1.85	21.2±6.2	20.1±3.8

Key takeaways

Formulation Strategy: Encapsulation into high-permeation vesicles (HPVs) composed of phospholipids and permeation enhancers.

•**Nanocarrier Characteristics**:

- ❑ Achieved nanoscale particle size.
- ❑ High encapsulation efficiency at 10% drug loading.

•**Formulation Type**: Fulvestrant-loaded HPVs incorporated into a gel base.

•**Performance**: In vitro release studies showed sustained drug release from the gel formulation.

•**Potential Advantage**: Enhanced local delivery and prolonged therapeutic effect due to sustained release

Thank You!