The relevance of nanotechnology, hepatoprotective agents in reducing the toxicity and augmenting the bioavailability of isotretinoin

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INTRODUCTION

Among several medications for dermatological application, isotretinoin (ITT) has been the most widely used. ITT has a unique importance in treating adult women with acne because it is not a hormone or an antibiotic. The **goal of the present study** was to formulate an effective **nanoemulsion** of isotretinoin, a drug for the disease, that would have enhanced **solubility and bioavailability.** Isotretinoin can have serious hepatotoxic effects with chronic administration, and to overcome these effects, **resveratrol and quercetin**, which are hepatoprotective agents, were incorporated into the formulations. Various essential oils, surfactants, and cosurfactants were examined to select the ingredients that would be essential for enhancing **solubility and permeation.**

METHODS

Pre-formulation Studies:
Evaluated ITT solubility in oils (tea tree, baobab), surfactants (Labrasol), and co-surfactants (Transcutol).

Optimized nanoemulsion components using Mixture Design (16 experimental runs).

Key variables:
Oil mixture (X_1), surfactant (X_2), co-surfactant (X_3).
Responses: Globule size, steady-state flux (J_{ss}), and permeability %.

Formulation & Characterization:
Prepared ITT-SNEDDS via spontaneous emulsification.
Measured globule size (Zetatrac analyzer), ex vivo permeation (rat skin), and in vitro release (dialysis membrane)

In Vivo Evaluation:
Assessed hepatoprotective effects in mice (14-day treatment).Measured liver biomarkers: AST, ALT, SOD, MDA, and GSH.

RESULTS &DISCUSSION

Key Results

Optimal SNEDDS Composition:
Oil mixture (0.15 g), Labrasol (0.6 g), Transcutol (0.25 g).

Globule size: 176.25 nm (predicted: 174.79 nm).

Permeability: 61.27% for ITT (ex vivo), 58.66% (in vitro).

Enhanced Bioavailability:
Steady-state flux (J_{ss}): 272.27 ± 7.12 mcg/cm²·h (ITT), 201.82 ± 9.97 mcg/cm²·h (RSV).

Hepatoprotection:
ITT-RSV-SNEDDS restored liver biomarkers to near-normal levels (AST: 20.16 U/L, ALT: 24.1 U/L vs. control).
Outperformed marketed products and ITT-alone formulations ($p < 0.05$)

RESULTS &DISCUSSION

The results reflect that SNEDDS formulations ITT-RSV and ITT-quercetin have high permeability through the rabbit skin. In addition to a significant protective effect against hepatotoxicity, especially for ITT-RSV SNEDDS while maintaining the good permeability and bioavailability of ITT.

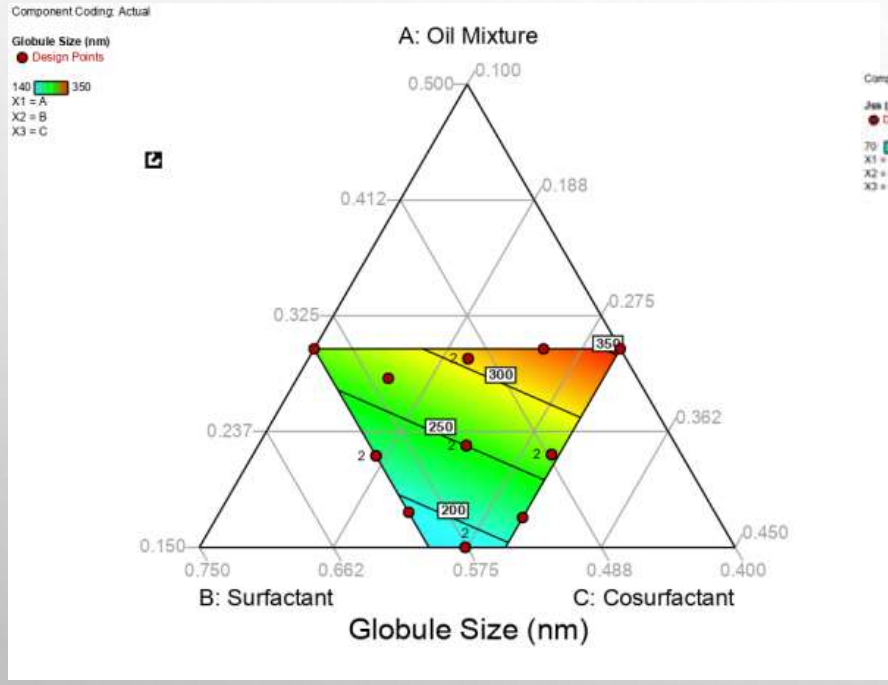
RESULTS &DISCUSSION

The effect of various formulation ingredients on hepatoprotective activity in comparison to marketed formulation.

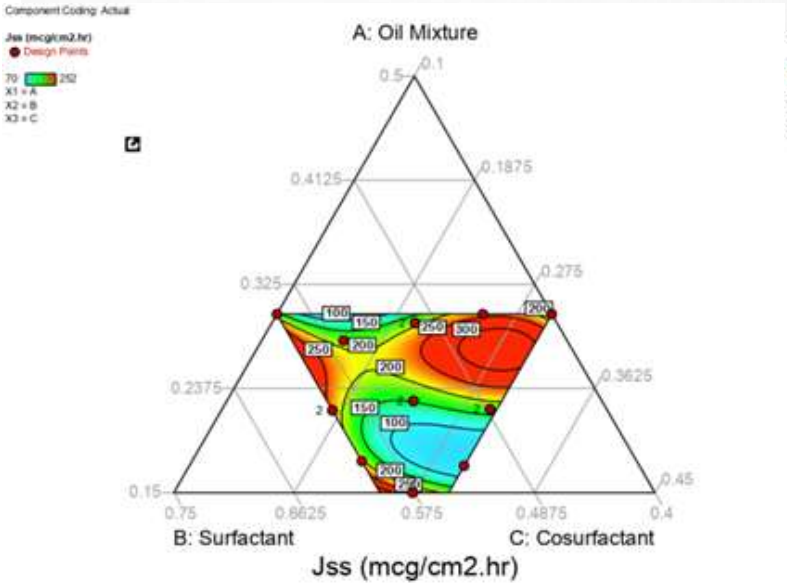
	AST	ALT	MDA	SOD	GSH
Groups	**Mean± SD**	**Mean± SD**	**Mean± SD**	**Mean± SD**	**Mean± SD**
G1 [Control Normal saline]	**19.8 ±1.89**	**21.85 ±1.47**	**0.682 ±0.029**	**421.8 ±2.8**	**636.47 ±16.56**
G2 [Distilled water + ITT (Oral)]	**38.5 ±3.26**	**46.57 ±4.54**	**1.28 ±0.025**	**307.3 ±3.5**	**383.71 ±13.8**
G3 [Distilled water + ITT (Topical)]	**31.5 ±3.4**	**38.26 ±3.76**	**0.82 ±0.021**	**326.1 ±1.9**	**445.09 ±17.48**
G4 [Formula (Part1) + ITT]	**92.5 ±6.3**	**65.3 ±4.2**	**0.92 ±0.028**	**349.3 ±2.5**	**383.3 ±2.4**
G5 [Formula (Part 1) + ITT + RSV]	**20.16 ±2.5**	**24.1 ±1.8**	**0.645 ±0.018**	**407.8 ±3.1**	**652.8 ±2.8**
G6 [Formula (Part1) + ITT + QRS]	**35.6 ± 3.9**	**31.3 ± 0.6**	**0.705 ± 0.016**	**366.3 ± 2.8**	**529 ± 2.4**
G7 [Marketed ITT cream]	**63.1 ±5.2**	**50.8 ±1.1**	**0.88 ±0.021**	**348.8 ±3.8**	**421.16 ±2.1**

RESULTS &DISCUSSION

Contour and 3-Dimensional response surface graphs for **A)** Globule size, **B)** JSS, and **C)** Percentage permeated.



[A]



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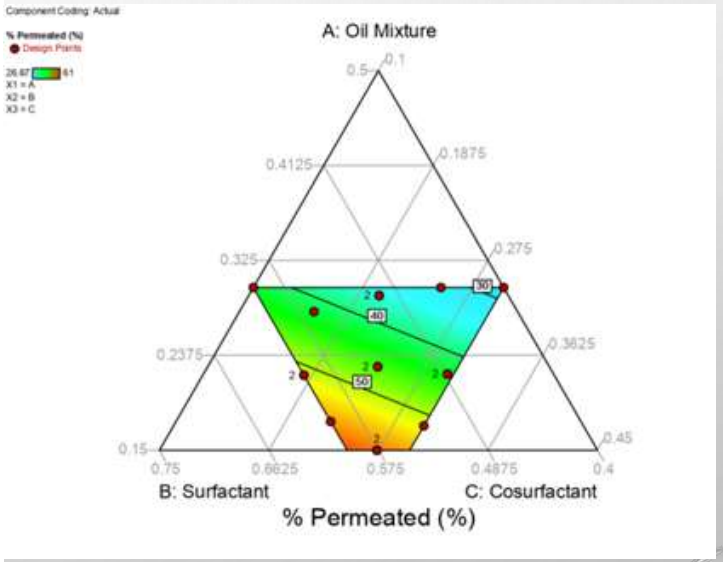

[C]

CONCLUSION

* SNEDDS significantly improved ITT solubility, permeation, and bioavailability.

* RSV integration mitigated hepatotoxicity, demonstrating synergistic therapeutic efficacy.

* **Clinical Implication:** A promising strategy for safe, effective acne management with minimized systemic side effects.