Simvastatin repurposing towards endometriosis management: The use of self-nanoemulsifying drug delivery system

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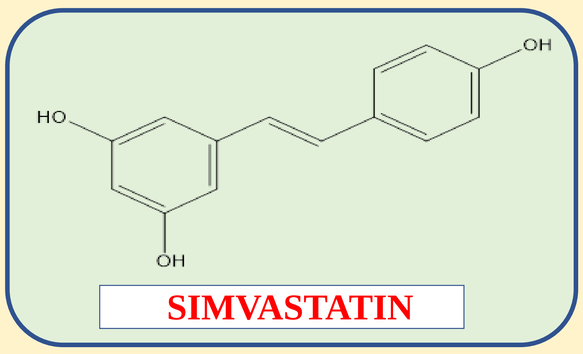
ABSTRACT

Endometriosis is a gynecological, chronic, benign, estrogen-dependent inflammatory disease and debilitating in nature. It causes infertility, excessive bleeding, dysmenorrhea, and dyspareunia. Marketed treatment for endometriosis involves progestins, danazol, hormone contraceptives, and GnRH analogs that cause severe side effects. Alternative treatment involves surgeries like laparoscopy and hysterectomy. The current repurposing of simvastatin was done voluntarily for the management of endometriosis. Self -nanoemulsifying drug delivery was systemically optimized for entrapping simvastatin.

INTRODUCTION

Simvastatin besides being a hypolipidemic drug has also been found to have pleiotropic effects (1). Repurposing of simvastatin has been done keeping in mind its pleiotropic effects which involve anti-inflammatory, anti-angiogenic, anti-oxidant, immunomodulatory, neuroprotective, and anti-cancer activity (2,3). Simvastatin is a lipophilic drug (log P> 4) that has low aqueous solubility which limits its bioavailability and therapeutic effectiveness. However, when it is formulated as a SNEDDS, it can be easily solubilized in the oil phase of the formulation, which improves its absorption and bioavailability. In addition, the lipophilic nature of simvastatin makes it compatible with the oil phase of SNEDDS, which can further enhance its solubility and stability in the formulation.



OBJECTIVE

To prepare simvastatin entrapped self-nanoemulsifying drug delivery system for the management of endometriosis.

METHODOLOGY

Systemic optimization of formula to prepare self-nanoemulsifying drug delivery system by QbD approach

Preformulation study

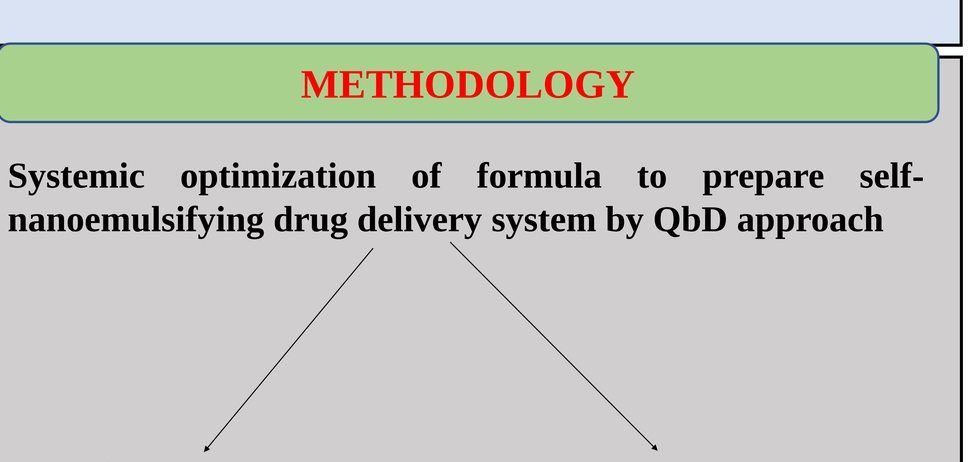
- RP-HPLC method development and validation
- Solubility study of simvastatin

Formulation Optimization by Formulation by design (FbD) approach

- Initial risk assessment
- Screening study
- Optimisation study

RESULT

Figure 1. Chromatogram of simvastatin



Retention Time (mins)	Drug
6.824 mins	Simvastatin

Table 1. System suitability parameters

Parameters	Simvastatin
Retention Time*	6.873
Tailing Factor	1.130
Number of Theoretical Plates	6849
% RSD of Peak Area*	0.43

RESULT

Figure 2. Calibration curve of simvastatin

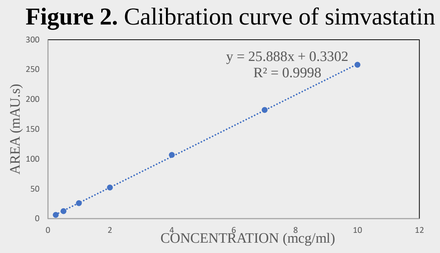


Table 2. Linearity, range, lod, loq

Analyte	Range (µg/ml)	Regression equation	Coefficient of determination (R^2)	LOD (µg/ml)	LOQ (µg/ml)	S.D of intercept	S.E of intercept
Simvastatin	0.25 - 10	y= 25.888x+0.3302	0.998	0.266	0.806	2.807	0.788

Table 3. Intra-day and inter-day precision for the developed method of simvastatin

Analyte	Known concentration level (µg/ml)	Found concentration level (µg/ml, mean ± SD, n=3)	Intra - day precision (Repeatability) %R.S.D
Intra-day precision			
Simvastatin	4	2.56 ± 0.004	0.18
	5	3 ± 0.038	1.28
	6	4.94 ± 0.004	0.09
Inter-day precision			
Simvastatin	4	2.55 ± 0.004	0.18
	5	3.60 ± 0.02	0.69
	6	4.93 ± 0.01	0.23

Figure 3. Solubility of simvastatin in different oils, surfactants, co-surfactants

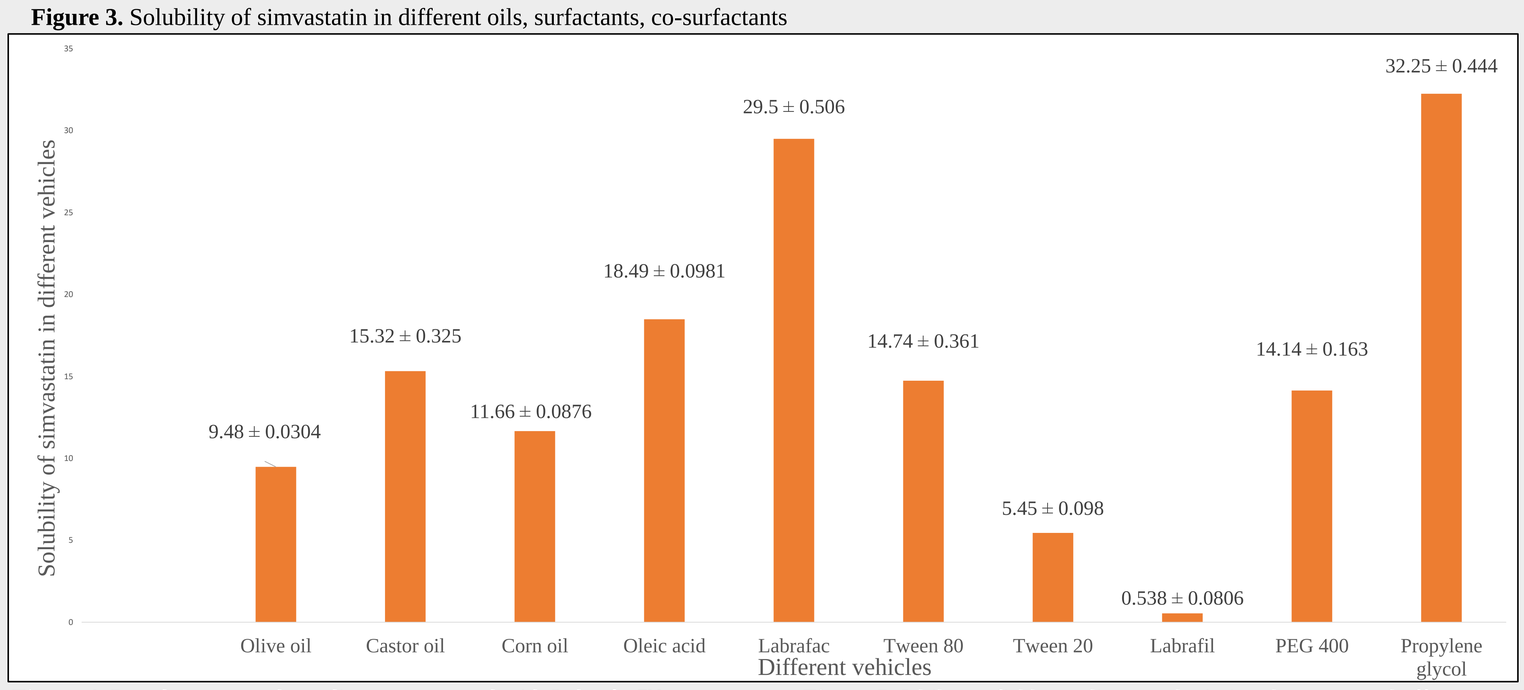


Figure 4. Pseudo-ternary-phase diagram prepared with Labrafac™ lipophile WL 134, Tween 80, and propylene glycol

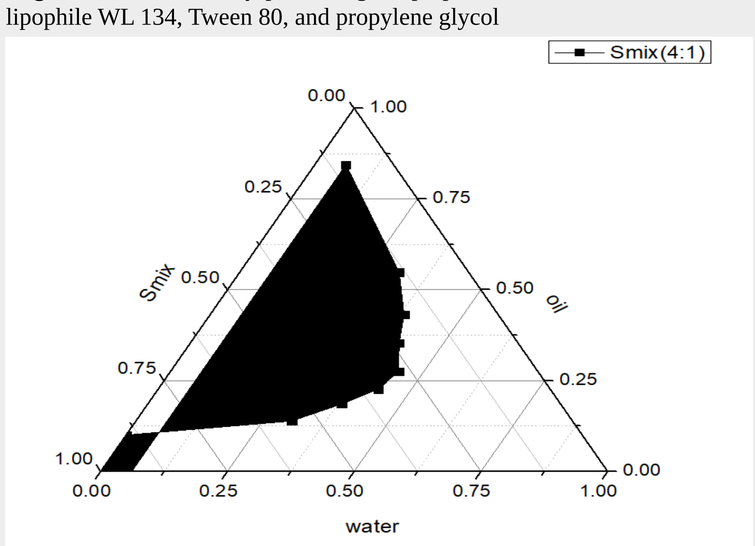
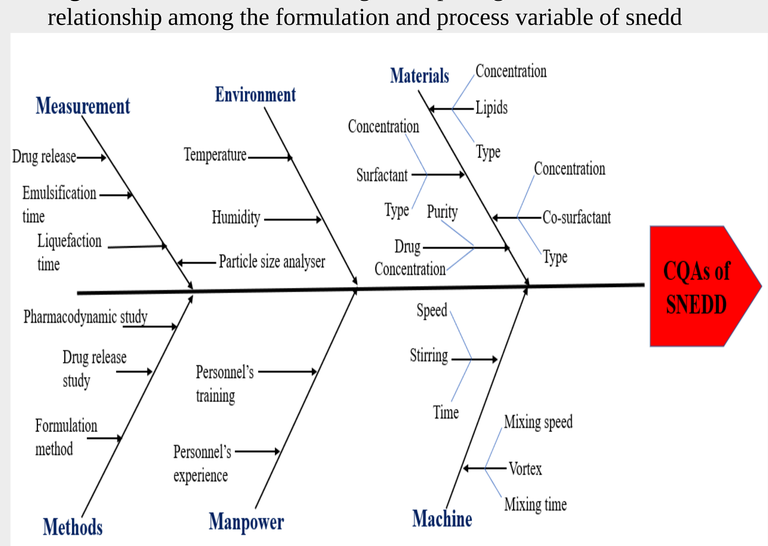


Figure 5. Ishikawa fishbone diagram depicting the cause and effect relationship among the formulation and process variable of snedd



DISCUSSION

Formulation by design (FbD) allowed to find out the formula to prepare self-nanoemulsifying drug delivery system.

CONCLUSION

Since simvastatin possesses pleiotropic effect, the current investigation deals with drug repurposing towards endometriosis management. The use of snedds was explored for this purpose and the formula of snedds was systemically optimized through the FbD approach.

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