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Original Article

Nanostructured Lipid Carrier-Based Hydrogel of Fenoprofen Calcium for Sustained Release: Optimization, Characterisation, and *in vitro* Evaluation

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ABSTRACT

Objectives: Fenoprofen Calcium (FEN) has short elimination half-life, frequent dosage administration and numerous gastrointestinal side effects on oral administration. The primary objective of this research was to synthesize optimized FEN-loaded Nanostructured Lipid Carriers (FEN-NLCs) using Box-Behnken design and develop its hydrogel with enhanced dissolution in conjunction with sustained drug release. **Materials and Methods:** FEN-NLCs were synthesized by solvent evaporation technique using Compritol 888 and oleic acid, optimised by Box-Behnken design and characterized by FTIR and HR-TEM. The FEN-NLC-hydrogel was evaluated for physicochemical characteristics and *in vitro* drug release study. **Results:** The desirability function of optimal formulation was found 0.874 with predicted values of 92.89 %w/w entrapment efficiency, 136.19 µg/cm^2/hour flux and 72.98%w/w yield. FEN-NLC-hydrogel was developed which illustrated pseudo-plastic flow behavior. FEN-hydrogel, PM-hydrogel and Fen-NLC-hydrogel exhibited cumulative drug release of 19.5%, 20.79% and 30.42% within 4 hr; 44.57%, 47.37% and 79.86% within 8 hr while 45.6%, 47.81% and 93.34% in 24 hr which revealed 2-folds enhancement in drug dissolution. This indicated poor *in vitro* drug release from plain drug-hydrogel with negligible increase in drug release after 8 hr. While Fen-NLC-hydrogel showed sustained increase in drug release till 24 hr. The *n*-value for peppas model was 0.8676 which showed anomalous phenomenon and sustained drug release from FEN-NLCs. **Conclusion:** The current research conclusively manifested that Fenoprofen Calcium loaded nanostructured lipid carriers-based hydrogel holds great prospective for providing sustained drug release.

Keywords: Fenoprofen Calcium, Box-Behnken design, Nanostructured lipid carriers, Sustained drug release.

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INTRODUCTION

Fenoprofen Calcium (FEN) is NSAID that is used to relieve discomfort, inflammation, and stiffness related with rheumatoid and osteoarthritis arthritis. However, its oral administration is often avoided owing to risk of serious gastrointestinal side effects including irritation, ulceration and gastric bleeding.[1] Its elimination half-life is 3 hr and therefore, regular doses are required to maintain an anti-inflammatory and analgesic effect.[2-4] The topical drug delivery has been considered to be safest, highly suitable, and cost-effective route of administration with superior patient compliance.[5,6] Moreover, NLCs are biocompatible with biological surface.[7-10] Moreover, on topical application of NLCs, solid and liquid lipids form a film that has occlusive qualities, effectively maintaining moisture in the skin for longer.[11] Topical NSAIDs tend to accumulate higher drug levels at inflamed site and do not require professional supervision for administration.[12-15] Therefore, manufacturing of FEN loaded Nanostructured Lipid Carriers (NLCs) and its incorporation into topical hydrogel could be advantageous for avoiding systemic adverse effects of Fenoprofen Calcium.

Compritol 888 ATO plays key role as solid lipid in NLCs manufacturing because of its capacity to encapsulate both hydrophilic and lipophilic drugs. Oleic acid is liquid lipid and its integration with solid lipid have potential to enhance loading via formation of imperfection in lipid lattice.[16] The primary objective of this research was to synthesize FEN-NLCs by solvent evaporation method using Compritol-888 and oleic acid and development of hydrogel of optimized NLC batch for achieving sustained drug release.

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MATERIALS AND METHODS

Materials

Fenoprofen Calcium was acquired from Suven Pharmaceuticals, Telangana, India. Compritol 888 and oleic acid were obtained from Sigma Aldrich. Analytical grade compounds were used for other investigations.

Experimental design

In this research, seventeen batches of NLCs were synthesized in accordance with BBD using combination of three factors at three levels and design analysis was executed to develop polynomial equation with the help of the Design-Expert software (Table 1). The design study was utilised to create polynomial equations between response parameter i.e. Y_1 (entrapment efficiency, % w/w), Y_2 (flux, µg/cm^2/hour) and Y_3 (yield, % w/w) and factors (X_1-X_3) as well as for optimising the formulation.[17-19]

Fabrication of FEN-NLCs

FEN-NLCs were developed using solvent evaporation method with slight modifications.[20-22] The drug and solid lipid were dissolved in dichloromethane while the liquid lipid was dissolved in acetone. These dispersions were blended to produce organic phase which was dropwise added to aqueous phase comprised of tween 80 and Brij 30 with continuous stirring at 70°C temperature for 4 hr in order to achieve solvent evaporation which resulted in production of semi-transparent nanoemulsion. This nanoemulsion was submerged into cold water/ice bath container for 2 hr to induce solidification of liquid globules as NLCs followed by freeze-drying for 24 hr in the presence lyoprotectants to increase the stability of NLCs. The differences in batches were managed by varying X_1 (solid lipid: liquid lipid), X_2 (stirring speed (rpm) and X_3 (emulsifier concentration (% v/v) at three different levels, *i.e.*, (75:25, 80:20, and 85:15), (1500, 2000, and 2500 rpm), and (1.5, 2, and 2.5 %v/v) as mentioned in Table 1. The other processing variables were kept constant to maintain consistency between batches.

Determination of Response Parameters

NLCs weighing 50 mg was extracted for 24 hr in phosphate buffer, pH 6.8 (PB, pH 6.8), centrifuged and estimated for FEN using UV-visible spectrophotometer at lambda max of 270 nm (n=3).[23] Percentage entrapment efficiency of FEN-NLCs was calculated using Eq. 1. The permeation study was executed in PB, pH 6.8 using Franz diffusion cell as described previously and steady state flux was calculated using Eq. 2.[20,24-28] The amount of dried FEN-NLCs was collected after synthesis of FEN-NLCs and precisely weighed.[29] Subsequently, percentage yield was calculated using Eq. 3.

$$\text{Drug Entrapment Efficiency (\%)} = \frac{\text{Actual content of drug}}{\text{Theoretically calculated amount of drug}} \times 100 \quad \text{Eq. (1)}$$

$$J_{ss}\,(Steady\ state\ flux) = \frac{dQ/dt}{A} \quad \text{Eq. (2)}$$

$$\text{Yield (\% w/w)} = \frac{\text{Weight of dried FEN-NLCs}}{\text{Weight of drug+lipids}} \times 100 \quad \text{Eq. (3)}$$

Optimization and Check Point Analysis of FEN-NLCs

An additional batch of FEN-NLCs explored by Design-Expert was manufactured utilizing optimized values of independent and dependent variables to validate optimization strategy. The response variables (Y1-Y3) for synthesized optimized FEN-NLCs were estimated and bias was calculated using Eq. 4 for validating the optimization strategy. The value of bias should be less than 5% for establishment of validation of optimization strategy.[30-32]

$$\text{\% Bias} = \frac{\text{Predicted value} - \text{Experimental value}}{\text{Predicted value}} \times 100 \quad \text{Eq. (4)}$$

Fourier Transforms Infrared Spectroscopy (FTIR) and High-Resolution Transmission Electron Microscope (HRTEM)

The samples of FEN, compritol 888 ATO, oleic acid, physical mixture and optimized FEN-NLCs were analysed for spectra by KBr method using FTIR spectrophotometer. HRTEM images of optimized FEN-NLCs were captured using Hitachi H-7500, Japan to observe the surface characteristics and shape of NLCs.

Incorporation of Optimized FEN-NLC into Hydrogel Dosage Form

Hydrogel was prepared by addition of few drops of triethanolamine to 1% w/v Carbopol 934 dispersion.[33] Optimized FEN-NLC (6.6% w/w) was incorporated into Carbopol dispersion. The addition of triethanolamine causes induction of hydrogel formation in Carbopol dispersion to obtain FEN-NLC-hydrogel.

Physical Characterization of Optimized FEN-NLC-Loaded Hydrogel

FEN-NLC-Hydrogel was examined for texture and homogeneity to confirm homogeneous characteristics.[34] Spreadability was determined by previously described procedure and was estimated from Eq. 5.[35,36]

$$\text{Spreadability} = (\text{Mass in Grams} \times \text{length of glass slide}) / \text{Time in seconds} \quad \text{Eq. (5)}$$

FEN-NLC-Hydrogel was examined for rheological behavior using Brookfield viscometer with S-64 spindle at different shear rates.[37] In order to evaluate thermodynamic stability of FEN-NLC-Hydrogel, two types of stress tests were conducted and then examined for phase separation. In centrifuge stress test, FEN-NLC-Hydrogel was centrifuged at 6,000 rpm for 30 min. Freeze-thaw cycle stress test comprised of three cycles of 24 hr at 45°C followed by 24 hr at -5°C.[38] For determination of drug

content, approximately one gram of FEN-NLC-Hydrogel was dispersed in PB, pH 6.8 and assessed spectroscopically at 270 nm.[39]

In vitro Drug Release Profile and Kinetics of Optimized FEN-NLC-Loaded Hydrogel

The drug release from optimized FEN-NLC-loaded hydrogel was performed using Franz diffusion cell. A dialysis membrane with a surface area of 2.54 cm^2 was positioned between the compartments of a Franz diffusion cell. A magnetic stirrer agitated 20 mL of pH 6.8 phosphate buffer in the acceptor compartment to prevent static surfaces and the temperature of the Franz diffusion cell chamber was controlled at 37±0.5°C. Approximately 0.5 mL of samples was collected and replenished with equal volume to maintain sink condition and afterwards samples were analysed at 270 nm with UV spectrophotometer. The release kinetic *i.e.* Higuchi, peppas, zero-and first-order models were applied to explore values of r^2 and drug release kinetic equations.[40]

Statistical Analysis

Statistical analysis for the design model was performed using ANOVA in Design-Expert software (*p<0.05). Additional analyses were conducted using GraphPad Prism. All results are presented as Mean±Standard Deviation.

RESULTS

Selection of Appropriate Design Model

As shown in Table 2, the difference among adjusted r^2 (0.966) and predicted r^2 (0.9528) as determined by model fit summary statistics was found less than 0.2 for quadratic model for Y_1. The p-value for design fit and sequential p-value for quadratic model was observed to be 0.0890 (p>0.05) and 0.0048 (p<0.05) for of Y_1; 0.0143 (p<0.05) and 0.0609 (p>0.05) for Y_2; and <0.0001 and 0.6928 (p>0.05) for Y_3. The difference between adjusted r^2 (0.9915) and predicted r^2 (0.9528) for Y_1, r^2 (0.9865) and r^2 (0.9216) for Y_2; and r^2 (0.9960) and r^2 (0.9903) for Y_3; as obtained by fit summary statistics, was less than 0.2.

Statistical Analysis of Response Parameters

Entrapment Efficiency (% EE) (Y_1)

The Y_1 was greatly influenced by X_1, X_2 and X_3 (p<0.05) as shown in Table 3. It has been determined from polynomial equation (Eq. 6) that the values of b_1, b_2 and b_3 for X_1, X_2 and X_3 (minutes) were -10.40, - 2.02 and 2.90, respectively and is also illustrated in 2-dimensional contour plots and 3-dimensional response surface plots as depicted in Figure 1.[41,42]

$$Y1=77.5 -10.40\ X1 -2.02\ X2 + 2.90\ X3 + 0.2625\ X1X2 + 0.4000\ X1X3 + 0.7200\ X2X3 – 1.75\ X1^2 – 0.7748\ X2^2 + 0.6828\ X3^2 \quad \text{Eq. (6)}$$

Flux (Y2)

The flux was strongly influenced by X_1-X_3 as indicated by p-value less than 0.05 (Table 3) this effect is graphically shown in Figure 2.[17] It has been observed from polynomial equation 7 that the values of b_1, b_2 and b_3 for X_1, X_2 and X_3 were 5.37, 14.92 and 12.05, respectively.

$$Y2=104.15 + 5.37\ X1 + 14.92\ X2 + 12.05\ X3 – 1.43\ X1X2 + 0.6950\ X1X3 + 5.11\ X2X3 + 2.75\ X1^2 - 0.7835\ X2^2 - 2.73\ X3^2 \quad \text{Eq. (7)}$$

Percentage Yield (Y_3)

The percentage yield of FEN-NLCs was strongly influenced by X_1 (solid lipid: liquid lipid) (p<0.0001), X_2 (stirring speed) and X_3 (emulsifier concentration) (p<0.05) as the main effect (as shown in Figure 3) and the quadratic effect of X_1^2, X_2^2 and X_3^2 on Y_3 was also manifested statistically significant as shown in Table 3. It has been observed from polynomial equation 8 that the values of b_1, b_2 and b_3 for X_1, X_2 and X_3 were 16.55, -1.95 and -1.23, respectively.

$$Y3=73.53 + 16.55\ X1 – 1.95\ X2 – 1.23\ X3 – 0.8925\ X1X2 + 0.5950X1X3 –0.2450X2X3 – 3.62\ X1^2 + 3.48\ X2^2 + 3.96\ X3^2 \quad \text{Eq. (8)}$$

Optimization and Validation

The optimal values of formulation composition and process variables for optimized FEN-NLC was found 83:17 of X_1 (solid lipid: liquid lipid), 2500 rpm X_2 (stirring speed) and 2.5% v/v X_3 (emulsifier concentration) having 0.874 desirability function as analysed by Design expert software as given in Figure 4. In addition to this, it gives predicted values of EE (%) (Y_1), flux (Y_2) and yield % (Y_3) which were 72.98%, 136.19 µg/cm^2/hour and 92.89%, respectively. The actual values of response variables of optimized FEN-NLCs synthesized as additional batch were 71.22% EE (%), 132.54 µg/cm^2/hour flux and 91.27 % yield. The percentage bias between actual and predicted values of response parameters was <5%.

Characterization of Fenoprofen Calcium Nanostructured Lipid Carriers

Fourier Transforms Infrared Spectroscopy Analysis

FTIR spectroscopy was utilised to demonstrate absence of significant interaction between the drug and the excipients and are shown in Figure 5 with values expressed in cm^{-1}. In the FTIR spectra of FEN (Figure 5a), the characteristic bands observed at 3643, 2980, 1577, and 1427 cm^{-1} corresponds to O-H stretching (s), C-H (s), O-C=O (s), and C-H bending, respectively which were in accordance with the reported finding. The bands at 2900 and 2854 cm^{-1} in the oleic acid spectrum correspond to asymmetric and symmetric C-H (s), respectively (Figure 5b). The sharp peak at 1700 cm^{-1} was due to the presence of C=O (s) which was in agreement with previous findings. FTIR spectrum

of Compritol 888 exhibited prominent peaks at 2848, 1729 and 1439 cm^{-1} for C-H (s), C=O (s) and C=C (s), correspondingly which was in accordance with reported finding (Figure 5c). In the spectrum of physical mixture, peaks at identical band groups are found, which indicates the absence of interaction between the drug and excipients (Figure 5d).[43-47] FTIR spectrum of FEN-NLCs displayed peaks at 3501, 2922 and 1729 (in cm^{-1}) for O-H, C-H and C=O stretching (Figure 5e). The variance in peak intensities may be caused by the overlap of certain functional groups for the specific band width.[48-52]

HR-Transmission Electron Microscopy

The optimized batch of FEN-NLCs demonstrated almost spherical size particles having size range of approximately 200 nm which is highly suitable particle size range for topical drug delivery as shown in Figure 6a.

Physical Characterization of optimized FEN-NLC-Loaded Hydrogel

Optimized FEN-NLC-loaded hydrogel was found cosmetically appealing, a smooth texture, and homogenous. The spreadability and pH were found to be 12±3 g.cm/sec and 6.1±0.2, which

Table 1: 3-factors 3-levels Box-Behnken design used for synthesis of various batches of FEN-NLCs.

Batch	X_1 (Solid lipid: Liquid lipid)	X_2 (Stirring Speed (rpm)	X_3 (Emulsifier concentration (% v/v)
1	75:25	1500	2
2	85:15	1500	2
3	75:25	2500	2
4	85:15	2500	2
5	75:25	2000	1.5
6	85:15	2000	1.5
7	75:25	2000	2.5
8	85:15	2000	2.5
9	80:20	1500	1.5
10	80:20	2500	1.5
11	80:20	1500	2.5
12	80:20	2500	2.5
13	80:20	2000	2
14	80:20	2000	2
15	80:20	2000	2
16	80:20	2000	2
17	80:20	2000	2

Table 2: Statistical analysis data for design model fit for Y_1-Y_3 of FEN-loaded nanostructured lipid carriers.

Source	Y	Sequential *p*-value	Lack of Fit *p*-value	Adjusted R^2	Predicted R^2
Linear	Y_1	<0.0001	0.0138	0.9702	0.9538
	Y_2	<0.0001	0.0042	0.9280	0.8788
	Y_3	<0.0001	0.0035	0.9101	0.8548
2FI	Y_1	0.7066	0.0090	0.9661	0.9097
	Y_2	0.0280	0.0114	0.9608	0.8793
	Y_3	0.9615	0.0018	0.8864	0.6670
Quadratic	Y_1	0.0048	0.0890	0.9915	0.9528
	Y_2	0.0143	0.0609	0.9865	0.9216
	Y_3	<0.0001	0.6928	0.9960	0.9903
Cubic	Y_1	0.0890	-	0.9966	-
	Y_2	0.0609	-	0.9956	-
	Y_3	0.6928	-	0.9950	-

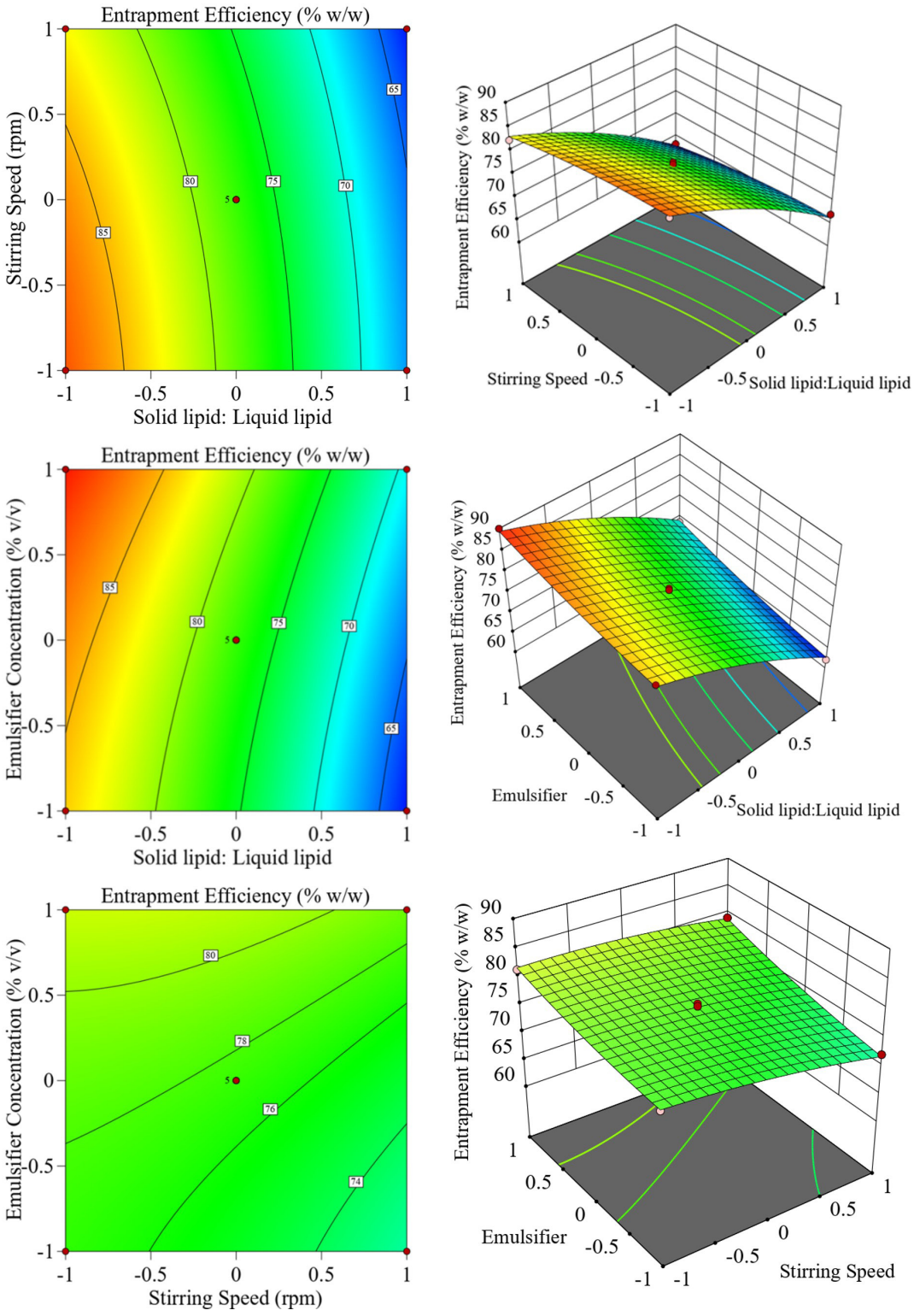

Figure 1: Graphical representation of design parameters for Entrapment Efficiency.

implied that its skin compatibility. The viscosity was found to be 7600, 6300, 4500, and 3400 centipoises, at rates of shear of 10, 20, 50, and 100 rpm, respectively. The drug content in FEN-NLCs-Hydrogel was determined to be 97.45%, suggesting that FEN was incorporated within the hydrogel.

In vitro Drug Release Kinetics of Optimized FEN-NLC-Loaded Hydrogel

FEN-Hydrogel, PM-Hydrogel and FEN-NLC-loaded hydrogel exhibited cumulative drug release of 19.5%, 20.79% and 30.42% within 4 hr; 44.57%, 47.37% and 79.86% within 8 hr while 45.6%, 47.81% and 93.34% within 24 hr, respectively. This indicated poor

Table 3: Analysis of variance data for Y_1 (Entrapment Efficiency), Y_2 (Flux value) and Y_3 (Percentage yield) of FEN-NLCs.

Source	Sum of Squares	d_f	Mean Square	F-value	p-value
Entrapment efficiency (Y_1)					
Model	985.72	9	109.52	209.02	<0.0001*
X_1	865.49	1	865.49	1651.76	<0.0001*
X_2	32.76	1	32.76	62.53	<0.0001*
X_3	67.16	1	67.16	128.18	<0.0001*
X_1X_2	0.2756	1	0.2756	0.5260	0.4918
X_1X_3	0.6400	1	0.6400	1.22	0.3056
X_2X_3	2.07	1	2.07	3.96	0.0870
X_1^2	12.89	1	12.89	24.60	0.0016*
X_2^2	2.53	1	2.53	4.82	0.0641
X_3^2	1.96	1	1.96	3.75	0.0942
Lack of Fit	2.84	3	0.9451	4.54	0.0890
Flux (µg/cm²/hour) Y2					
Model	3349.45	9	372.16	131.20	<0.0001*
X_1	231.02	1	231.02	81.44	<0.0001*
X_2	1780.25	1	1780.25	627.61	<0.0001*
X_3	1160.90	1	1160.90	409.26	<0.0001*
X_1X_2	8.15	1	8.15	2.87	0.1339
X_1X_3	1.93	1	1.93	0.6811	0.4364
X_2X_3	104.55	1	104.55	36.86	0.0005*
X_1^2	31.93	1	31.93	11.26	0.0122*
X_2^2	2.58	1	2.58	0.9112	0.3716
X_3^2	31.29	1	31.29	11.03	0.0127*
Lack of Fit	16.16	3	5.39	5.82	0.0609
Yield (% w/w) Y3					
Model	2406.55	9	267.39	448.05	<0.0001*
X_1	2192.21	1	2192.21	3673.32	<0.0001*
X_2	30.30	1	30.30	50.78	0.0002*
X_3	12.15	1	12.15	20.36	0.0028*
X_1X_2	3.19	1	3.19	5.34	0.0541
X_1X_3	1.42	1	1.42	2.37	0.1674
X_2X_3	0.2401	1	0.2401	0.4023	0.5461
X_1^2	55.11	1	55.11	92.34	<0.0001*
X_2^2	50.91	1	50.91	85.31	<0.0001*
X_3^2	66.19	1	66.19	110.90	<0.0001*
Lack of Fit	1.17	3	0.3890	0.5168	0.6928

*Statistically significant; d_f: degree of freedom.

in vitro drug release from plain drug-hydrogel with negligible increase in drug release after 8 hr. While Fen-NLC-Hydrogel showed sustained increase in drug release till 24 hr and attained maximum drug release of 93.34% over the period of 24 hr as observed in Figure 6b. The regression equation for zero-order, first-order, Higuchi and Peppas models were

y=4.1875x+14.322 (r2=0.7458); y=-0.0558x+1.9849 (r2=0.8732); y=25.453x-15.264 (r2=0.869); and y=0.8676x+0.9215 (r2=0.921),

respectively, with n-value of 0.867, showed that the Peppas model was best fitted with anomalous release.[53]

DISCUSSION

The quadratic equation 6 showed that X_1 and X_2 produced antagonistic effect on Y_1 while X_3 produced synergistic effect on Y_1. Figure 1 showed that increasing the solid lipid: liquid lipid ratio in FEN-NLCs caused decrease in %EE. This illustrated that rise in the amount of liquid lipid in formulation may cause increase in percentage entrapment efficiency. This might be the result of the huge disruption of the crystal structure caused by the inclusion of liquid lipids into solid lipids. Increased defects in the crystal lattice provide more space for drug molecules, which eventually cause improvement in the efficiency of drug entrapment.[41,42] The polynomial equation 7 showed that X_1, X_2 and X_3 produced synergistic effect on Y_2. Figure 2 showed the synergistic effect of stirring speed (X_2) on flux could be due to the decrease in NLC

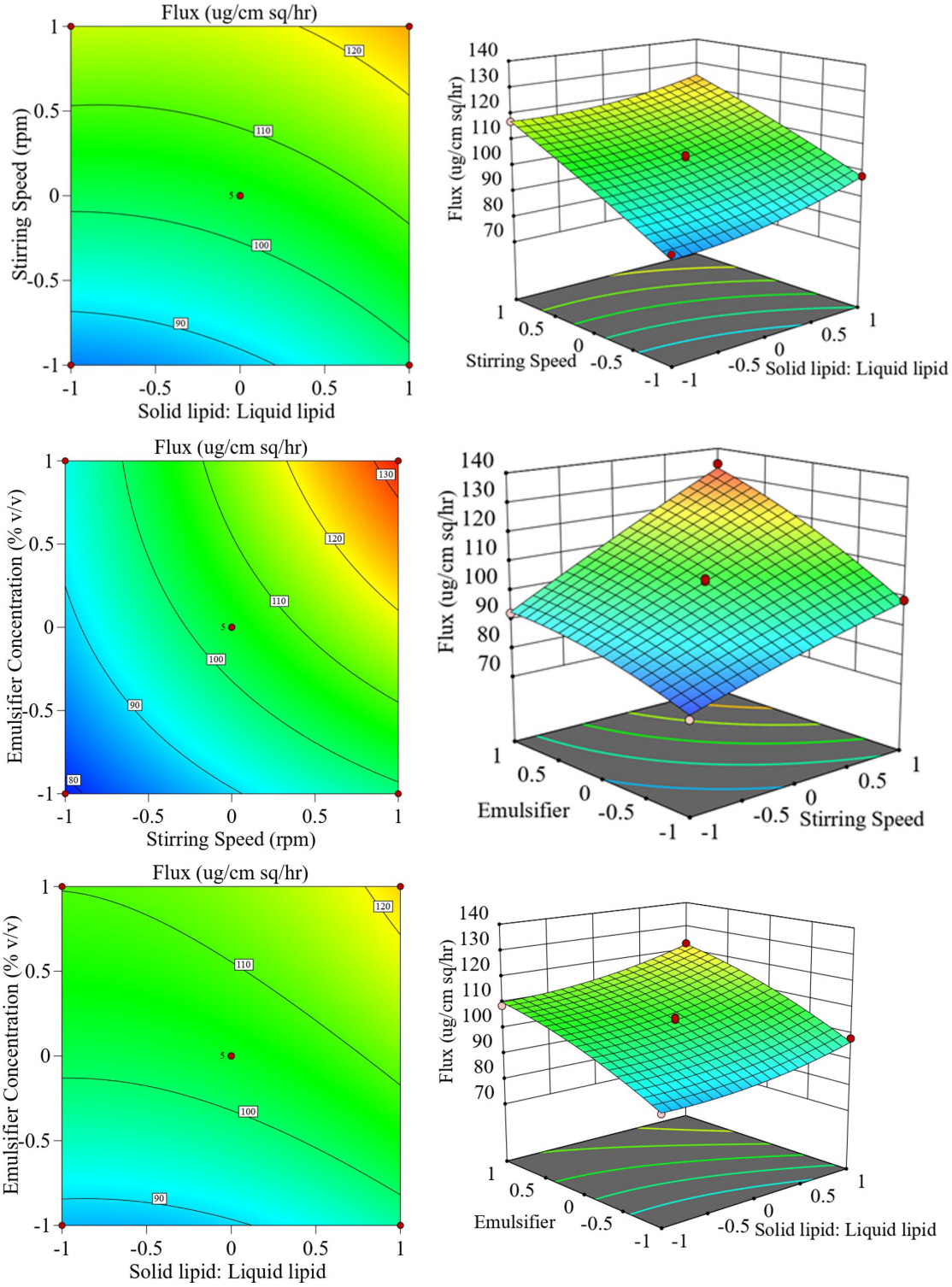

Figure 2: Manifestation of change in factors at various levels versus flux of FEN-NLCs.

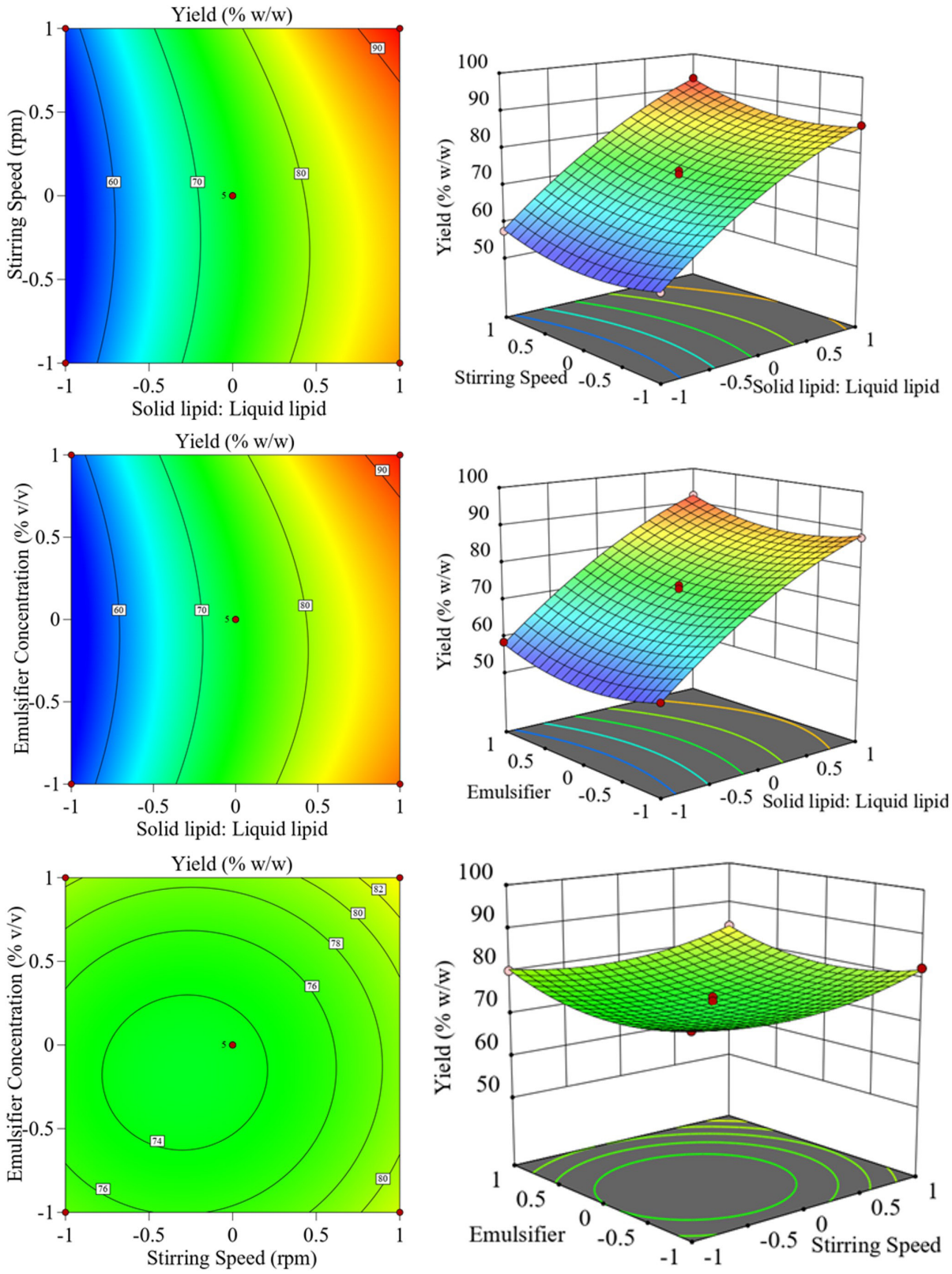

Figure 3: Elucidation of influence of X1, X2 and X3 on percentage yield of FEN-NLCs.

particle size as stirring speed increases. The smaller particles could permeate more effectively leading to higher flux value. The synergistic effect of emulsifier concentration (X_3) on flux could be attributed to emulsifying characteristics of emulsifier used in manufacturing of FEN-NLC which tends to improve the solubility and permeability of FEN.[17] Polynomial equation 8 demonstrated that augmenting the quantity of X_1 increased the value of Y_3 while increasing the amount of X_2 and X_2 decreased the value of

Y_3 (Figure 3). The experimental values of response variables for optimized FEN-NLC were in compliance to predicted values with percentage bias for Y1, Y2 and Y3 of 2.41, 2.68 and 1.74, respectively (less than 5%) which validated the authenticity of optimization strategy of design model (Figure 4). FTIR spectrum of drug and excipients authenticated the presence of characteristic functional groups (Figures 5a-c). In the FTIR spectrum of physical mixture (Figure 5d), the characteristics peaks of drug and excipients were retained which indicated compatibility of drug and excipients. FTIR spectra of nanostructured lipid carriers showed successful drug incorporation into FEN-NLCs (Figure 5e).[43,49,52] High resolution transmission electron microscopy of optimized FEN-NLCs showed spherical structures (Figure 6a). The viscosity of FEN-NLCs loaded topical hydrogel decreased as shear rate was increased. The observed decrease in viscosity may be attributed to the disentanglement and alignment of hydrogel molecules in the direction of flow under shear stress. This property facilitates the spreading of the hydrogel upon topical application, enabling efficient coverage and absorption. Fen-NLC-Hydrogel exhibited cumulative drug release of 30.42% within 4 hr; 79.86% within 8 hr while 93.34% within 24 hr which indicated sustained drug release till 24 hr which might be attributable to drug diffusion through the lipid and erosion of lipid matrix (Figure 6b). This signified that synthesis of NLC of FEN posed approximately 2-folds increase in dissolution in conjunction with sustained drug release till 24 hr. The '*n-value*' for peppas model was 0.867 which indicated anomalous drug release mechanism from NLC-Hydrogel which is the combination of diffusion and erosion from lipid matrix.[53]

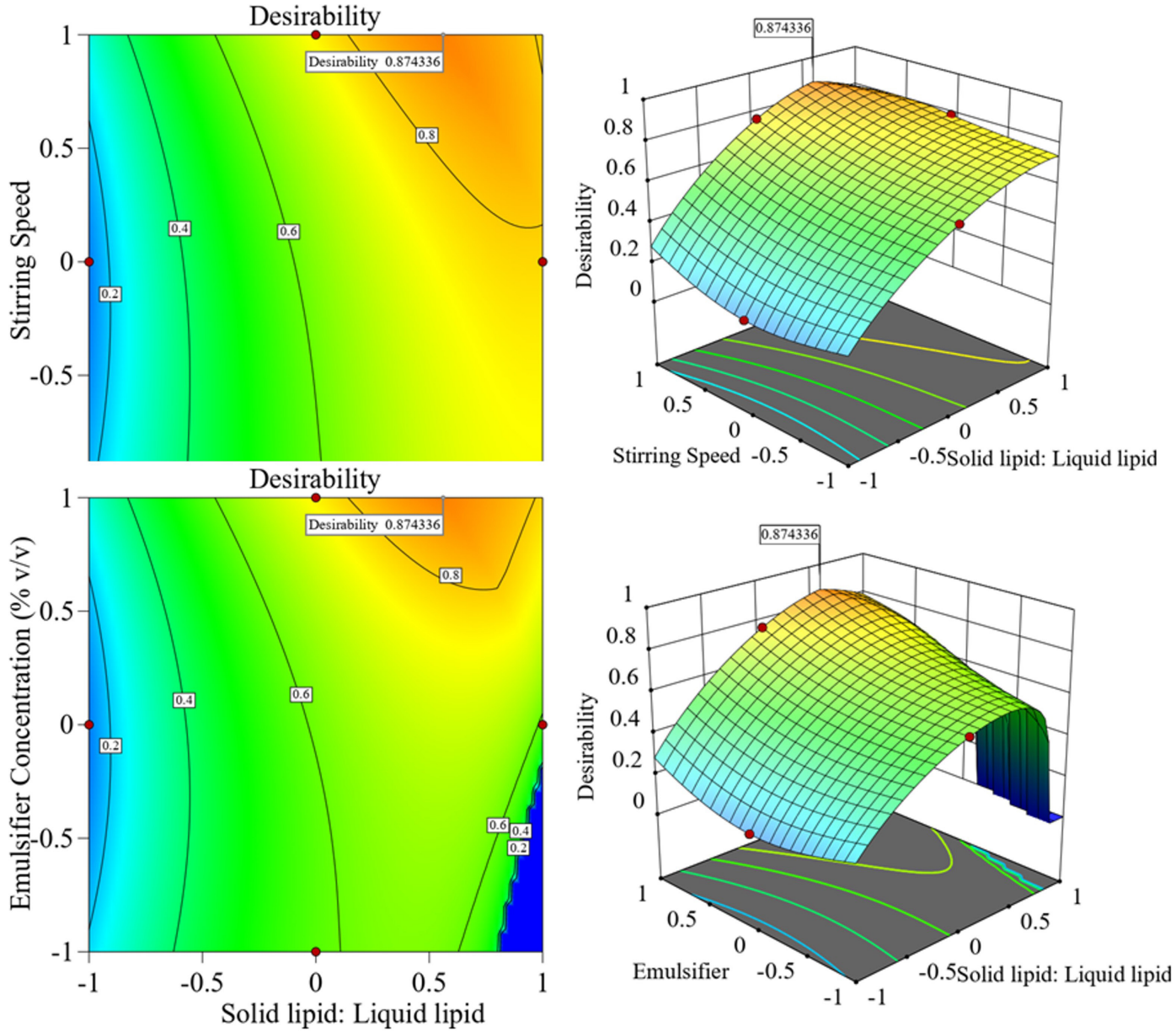

Figure 4: The graphical display of desirability function of FEN-NLC.

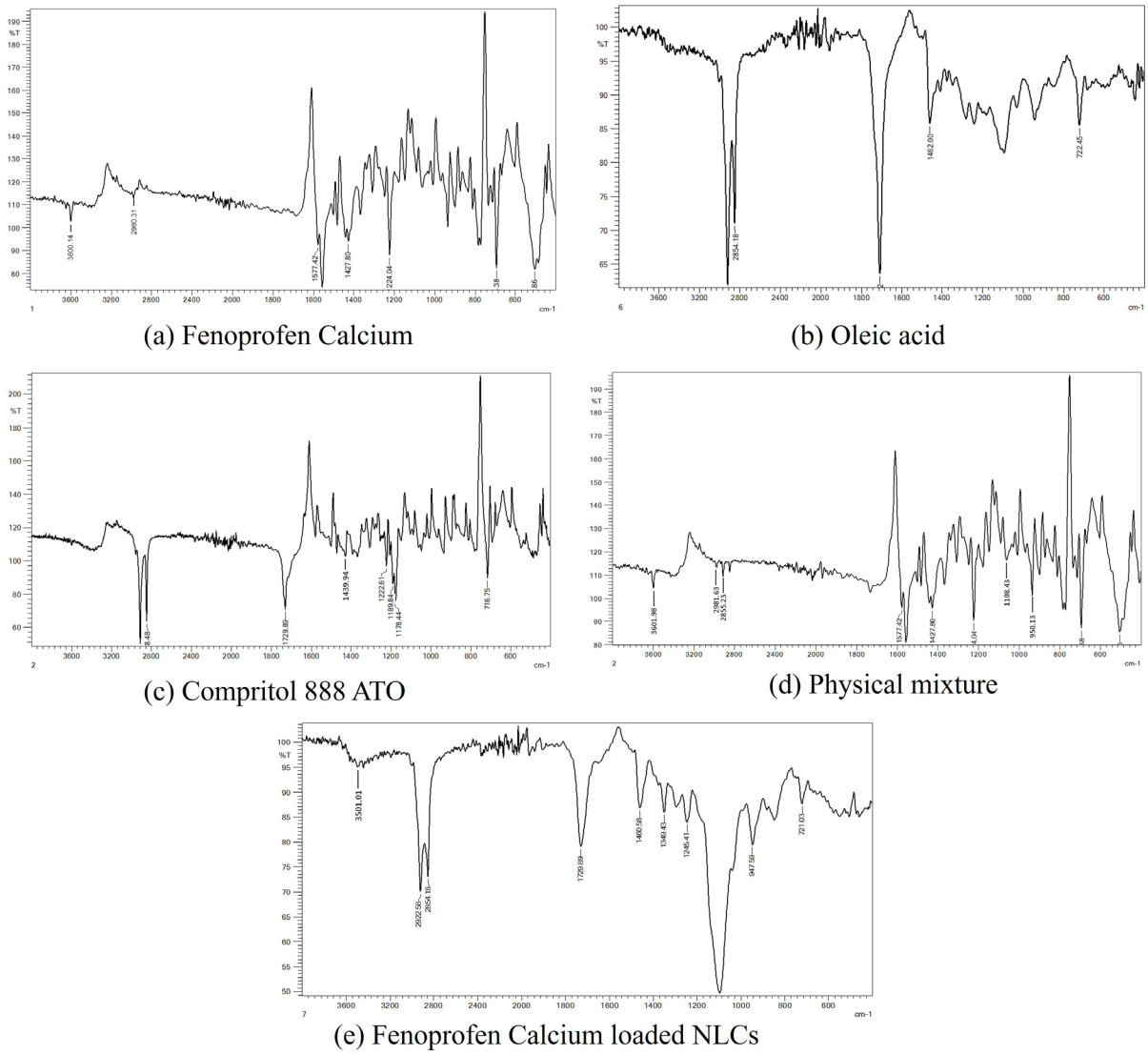

Figure 5: FTIR spectra of (a) Fenoprofen Calcium, (b) Oleic acid, (c) Compritol 888, (d) Physical mixture, (e) Fenoprofen Calcium loaded nanostructured lipid carriers.

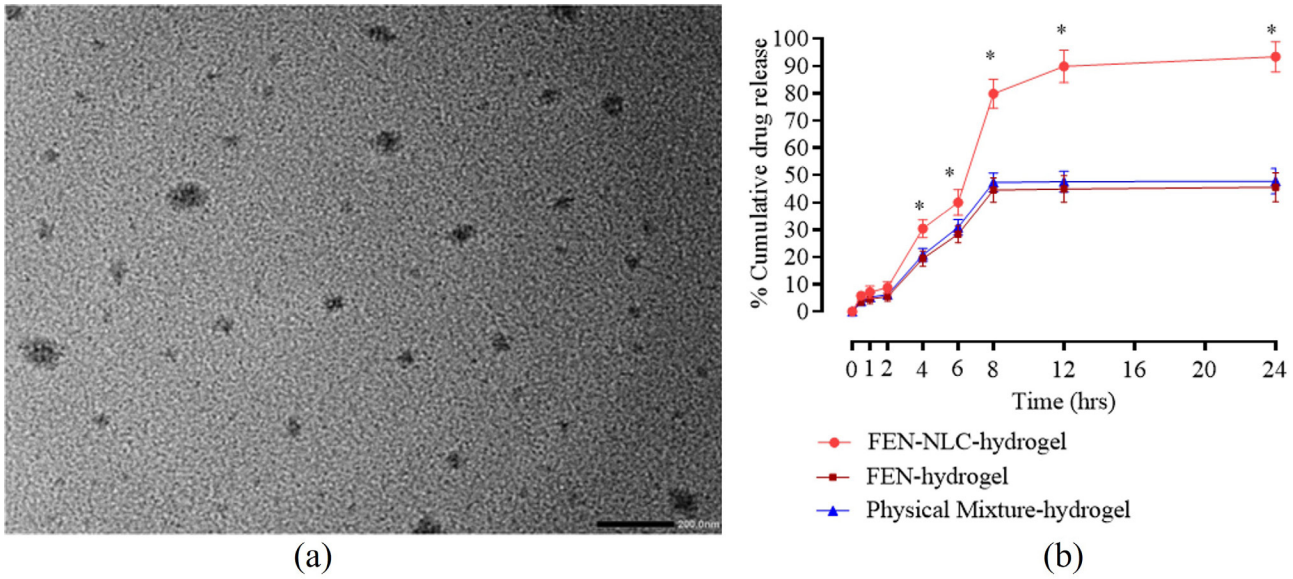

Figure 6: (a) HRTEM images of FEN-NLCs and (b) *In vitro* drug release pattern from FEN-hydrogel, PM-hydrogel and FEN-NLCs-hydrogel.

CONCLUSION

Box-Behnken design was successfully applied in revealing optimized values of composition and process variables for manufacturing of FEN-NLCs. The research revealed that quadratic model was typical to demonstrate the statistical analysis of FEN-NLCs as indicated by insignificant *p*-value for lack of fit ($p>0.05$) and significant *p*-value for model ($p<0.05$). The optimal values of composition and process variables for optimized FEN-NLC was found 83:17 (ratio of solid/liquid lipid), stirring at 2500 rpm speed and 2.5% v/v emulsifier concentration having desirability function of 0.874 with predicted values of 72.98% w/w entrapment efficiency (Y_1), 136.19 µg/cm^2/hour flux value (Y_2) and 92.89% w/w yield (Y_3), respectively. The optimized FEN-NLCs based hydrogel dosage form illustrated pseudo-plastic flow behavior. The absence of phase separation demonstrated thermodynamic stability of FEN-NLCs-Hydrogel. *In vitro* dissolution of FEN-NLC-Hydrogel revealed that synthesis of NLC of FEN posed approximately 2-folds increase in dissolution in conjunction with sustained drug release till 24 hr which suggested homogeneous entrapment and even dispersion of drug in the lipid matrix. FEN-NLC-Hydrogel showed anomalous drug release phenomenon. The present research conclusively evidenced that FEN-NLC-Hydrogel holds enormous future as topical dosage form for achieving sustained as well as enhanced drug release.

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ABBREVIATIONS

FEN: Fenoprofen Calcium; **FEN-NLCs:** Fenoprofen Calcium Loaded Nanostructured Lipid Carriers; **NLCs:** Nanostructured Lipid Carriers; **P_{app}:** Permeability Coefficient; **J_{ss}:** Steady State flux; **FTIR:** Fourier transforms infrared spectroscopy; **HRTEM:** High Resolution Transmission Electron Microscope; **EE:** Entrapment Efficiency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This research study aims to synthesize optimized FEN-NLCs-hydrogel to enhance *in vitro* drug dissolution in conjunction with sustained drug release behaviour on topical administration of semisolid dosage form of FEN-NLCs-hydrogel. BBD-based optimized FEN-NLCs were incorporated into FEN-NLC-hydrogel which illustrated pseudo-plastic flow behavior. FEN-Hydrogel, PM-Hydrogel and FEN-NLC-Hydrogel exhibited cumulative drug release of 19.5%, 20.79% and 30.42% within 4 hr; 44.57%, 47.37% and 79.86% within 8 hr while 45.6%, 47.81% and 93.34% in 24 hr. This indicated poor *in vitro* drug release from plain drug-hydrogel with negligible increase in drug release after 8 hr. While Fen-NLC-Hydrogel showed sustained increase in drug release for 24 hr. This study concluded that FEN-NLCs-based hydrogel exhibits significant potential for achieving sustained drug release, offering a promising approach for improved therapeutic outcomes.

REFERENCES

1. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821-47.
2. Farghaly DA, Aboelwafa AA, Hamza MY, Mohamed MI. Topical delivery of fenoprofen calcium via elastic nano-vesicular spanlastics: Optimization using experimental design and *in vivo* evaluation. AAPS PharmSciTech. 2017;18:2898-909. doi: 10.1208/s12249-017-0771-8
3. Yasir M, Chauhan I, Zafar A, Verma M, Noorulla KM, Tura AJ, *et al.* Buspirone loaded solid lipid nanoparticles for amplification of nose to brain efficacy: Formulation development, optimization by Box-Behnken design, *in vitro* characterization and *in vivo* biological evaluation. J Drug Deliv Sci Technol. 2021;61:102164. doi: 10.1016/j.jddst.2020.102164
4. Farghaly DA, Aboelwafa AA, Hamza MY, Mohamed MI. Microemulsion for topical delivery of fenoprofen calcium: *in vitro* and *in vivo* evaluation. J Liposome Res. 2018;28(2):126-36. doi: 10.1080/08982104.2017.1281951
5. Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. J Pharm Sci. 2014;103(1):29-52. doi: 10.1002/jps.23773
6. Chauhan I, Yasir M, Verma M, Singh AP. Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. Adv Pharm Bull. 2020;10(2):150. doi: 10.34172/apb.2020.021
7. Sharma N, Zahoor I, Sachdeva M, Subramaniyan V, Fuloria S, Fuloria NK, *et al.* Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies. Environ Sci Pollut Res. 2021; 1-8. doi: 10.1007/s11356-021-16570-y
8. Syed Azhar SN, Ashari SE, Zainuddin N, Hassan M. Nanostructured lipid carriers-hydrogels system for drug delivery: Nanohybrid technology perspective. Molecules. 2022;27(1):289. doi: 10.3390/molecules27010289
9. Gundogdu E, Demir ES, Ekinci M, Ozgenc E, Ilem-Ozdemir D, Senyigit Z, *et al.* An innovative formulation based on nanostructured lipid carriers for imatinib delivery: Pre-formulation, cellular uptake and cytotoxicity studies. Nanomaterials. 2022;12(2):250. doi: 10.3390/nano12020250
10. Varela-Fernández R, García-Otero X, Díaz-Tomé V, Regueiro U, López-López M, González-Barcia M, *et al.* Lactoferrin-loaded nanostructured lipid carriers (NLCs) as a new formulation for optimized ocular drug delivery. Eur J Pharm Biopharm. 2022;172:144-56. doi: 10.1016/j.ejpb.2022.02.010
11. Ghate VM, Lewis SA, Prabhu P, Dubey A, Patel N. Nanostructured lipid carriers for the topical delivery of tretinoin. Eur J Pharm Biopharm. 2016;108:253-61. doi: 10.1016/j.ejpb.2016.07.026
12. Patel D, Dasgupta S, Dey S, Ramani YR, Ray S, Mazumder B. Nanostructured lipid carriers (NLC)-based gel for the topical delivery of aceclofenac: preparation, characterization, and *in vivo* evaluation. Sci Pharm. 2012;80(3):749. doi: 10.3797/scipharm.1202-12
13. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm. 2008;346(1-2):124-32. doi: 10.1016/j.ijpharm.2007.05.060
14. Brune K, Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J Pain Res. 2015;8:105-18. doi: 10.2147/JPR.S75160
15. Sacha M, Faucon L, Hamon E, Ly I, Haltner-Ukomadu E. *Ex vivo* transdermal absorption of a liposome formulation of diclofenac. Biomed Pharmacother. 2019;111:785-90. doi: 10.1016/j.biopha.2018.12.079
16. Alhalmi A, Amin S, Khan Z, Beg S, Al Kamaly O, Saleh A, *et al.* Nanostructured lipid carrier-based codelivery of raloxifene and naringin: formulation, optimization, *in vitro*, *ex vivo*, *in vivo* assessment, and acute toxicity studies. Pharmaceutics. 2022;14(9):1771. doi: 10.3390/pharmaceutics14091771
17. Moghddam SM, Ahad A, Aqil M, Imam SS, Sultana Y. Optimization of nanostructured lipid carriers for topical delivery of nimesulide using Box–Behnken design approach. Artif Cells Nanomed Biotechnol. 2017;45(3):617-24. doi: 10.3109/21691401.2016.1167699

18. Sharma A, Singh AP, Harikumar SL. Development and optimization of nanoemulsion based gel for enhanced transdermal delivery of nitrendipine using box-behnken statistical design. Drug Dev Ind Pharm. 2020;46(2):329-42. doi: 10.1080/03639045.2020.1721527
19. Pradhan M, Singh D, Singh MR. Fabrication, optimization and characterization of Triamcinolone acetonide loaded nanostructured lipid carriers for topical treatment of psoriasis: Application of Box Behnken design, *in vitro* and *ex vivo* studies. J Drug Deliv Sci Technol. 2017;41:325-33. doi: 10.1016/j.jddst.2017.07.024
20. Zahoor I, Sharma N, Behl T, Singh S. Diagnostic analysis and graphical optimization of fenoprofen calcium-loaded nanostructured lipid carriers using design of experiments. Int J Pharm Qual Assur. 2022;13(3):240-46. DOI: 10.25258/ijpqa.13.3.03
21. Chen P, Zhang H, Cheng S, Zhai G, Shen C. Development of curcumin loaded nanostructured lipid carrier based thermosensitive *in situ* gel for dermal delivery. Colloids Surf A: Physicochem Eng Asp. 2016;506:356-62. doi: 10.1016/j.colsurfa.2016.06.054
22. Chen H, Wang Y, Zhai Y, Zhai G, Wang Z, Liu J. Development of a ropivacaine-loaded nanostructured lipid carrier formulation for transdermal delivery. Colloids Surf A: Physicochem Eng Asp. 2015;465:130-6. doi: 10.1016/j.colsurfa.2014.10.046
23. Halder A, Sa B. Preparation and *in vitro* evaluation of polystyrene-coated diltiazem-resin complex by oil-in-water emulsion solvent evaporation method. AAPS PharmSciTech. 2006;7:E105-12. doi: org/10.1208/pt070246
24. Sanna V, Gavini E, Cossu M, Rassu G, Giunchedi P. Solid lipid nanoparticles (SLN) as carriers for the topical delivery of econazole nitrate: *in vitro* characterization, *ex vivo* and *in vivo* studies. J Pharm Pharmacol. 2007;59(8):1057-64. doi: 10.1211/jpp.59.8.0002
25. B. Sánchez A, C. Calpena A, Mallandrich M, Clares B. Validation of an *ex vivo* permeation method for the intestinal permeability of different BCS drugs and its correlation with Caco-2 *in vitro* experiments. Pharmaceutics. 2019;11(12):638. doi: 10.3390/pharmaceutics11120638
26. Khafagy ES, Abu Lila AS, Sallam NM, Sanad RA, Ahmed MM, Ghorab MM, *et al.* Preparation and characterization of a novel mucoadhesive carvedilol nanosponge: a promising platform for buccal anti-hypertensive delivery. Gels. 2022;8(4):235. doi: 10.3390/gels8040235
27. Salunkhe SS, Bhatia NM, Pokharkar VB, Thorat JD, Bhatia MS. Topical delivery of Idebenone using nanostructured lipid carriers: evaluations of sun-protection and anti-oxidant effects. J Pharm Investig. 2013;43:287-303. doi: 10.1007/s40005-013-0079-y
28. Ameeduzzafar, Qumber M, Alruwaili NK, Bukhari SN, Alharbi KS, Imam SS, *et al.* BBD-based development of itraconazole loaded nanostructured lipid carrier for topical delivery: *in vitro* evaluation and antimicrobial assessment. J Pharm Innov. 2021;16:85-98. doi: 10.1007/s12247-019-09420-5
29. Sukhbir S, Yashpal S, Sandeep A. Development and statistical optimization of nefopam hydrochloride loaded nanospheres for neuropathic pain using Box–Behnken design. Saudi Pharm J. 2016;24(5):588-99. doi: 10.1016/j.jsps.2015.03.020
30. Dudhipala N, Janga KY. Lipid nanoparticles of zaleplon for improved oral delivery by Box–Behnken design: optimization, *in vitro* and *in vivo* evaluation. Drug development and industrial pharmacy. 2017;43(7):1205-14. doi: 10.1080/03639045.2017.1304957
31. Alam S, Aslam M, Khan A, Imam SS, Aqil M, Sultana Y, *et al.* Nanostructured lipid carriers of pioglitazone for transdermal application: from experimental design to bioactivity detail. Drug Deliv. 2016;23(2):601-9. doi: 10.3109/10717544.2014.923958
32. Pandey SS, Patel MA, Desai DT, Patel HP, Gupta AR, Joshi SV, *et al.* Bioavailability enhancement of repaglinide from transdermally applied nanostructured lipid carrier gel: optimization, *in vitro* and *in vivo* studies. J Drug Deliv Sci Technol. 2020;57:101731. doi: 10.1016/j.jddst.2020.101731
33. Patel NA, Patel NJ, Patel RP. Formulation and evaluation of curcumin gel for topical application. Pharm Dev Technol. 2009;14(1):83-92. doi: 10.1080/10837450802409438
34. Chen MX, Alexander KS, Baki G. Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application. Journal of pharmaceutics. 2016;2016(1):5754349. doi: 10.1155/2016/5754349
35. Chaudhary B, Verma S. Preparation and evaluation of novel *in situ* gels containing acyclovir for the treatment of oral herpes simplex virus infections. Sci World J. 2014;2014(1):280928. doi: 10.1155/2014/280928
36. Pawar DP, Shamkuwar PB. Formulation and evaluation of herbal gel containing Lantana camara leaves extract. Asian J Pharm Clin Res. 2013;6(3):122-4.
37. Shukla R, Tiwari G, Tiwari R, Rai AK. Formulation and evaluation of the topical ethosomal gel of melatonin to prevent UV radiation. Journal of cosmetic dermatology. 2020;19(8):2093-104. doi: 10.1111/jocd.13251
38. Tayel SA, El-Nabarawi MA, Tadros MI, Abd-Elsalam WH. Promising ion-sensitive *in situ* ocular nanoemulsion gels of terbinafine hydrochloride: design, *in vitro* characterization and *in vivo* estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits. Int J Pharm. 2013;443(1-2):293-305. doi: 10.1016/j.ijpharm.2012.12.049
39. Al-Sarraf MA, Hussein AA, Al-Sarraf ZA. Comparison Between Conventional Gel and Nanostructured Lipid Carrier Gel of Zaltoprofen: Preparation and *In vitro*/*Ex vivo*. Evaluation Technol J. 2021;11(3):988-95.
40. Maanvizhi S, Iyyappan V, Bhavishi PG. *In vitro* release study of Diclofenac sodium from topical gel formulations using diffusion cell. Res J Pharm Technol. 2020;13(6):2901-5. doi: 10.5958/0974-360X.2020.00517.X
41. Moghddam SM, Ahad A, Aqil M, Imam SS, Sultana Y. Optimization of nanostructured lipid carriers for topical delivery of nimesulide using Box–Behnken design approach. Artificial cells, Nanomedicine, and Biotechnology. 2017;45(3):617-24. doi: 10.3109/21691401.2016.1167699
42. Jazuli I, Nabi B, Alam T, Baboota S, Ali J. Optimization of nanostructured lipid carriers of lurasidone hydrochloride using box-behnken design for brain targeting: *in vitro* and *in vivo* studies. J Pharm Sci. 2019;108(9):3082-90. doi: 10.1016/j.xphs.2019.05.001
43. Ammar HO, Makram TS, Mosallam S. Effect of polymers on the physicochemical properties and biological performance of fenoprofen calcium dihydrate-triacety l-β-cyclodextrin complex. Pharmaceutics. 2017;9(3):23. doi: 10.3390/pharmaceutics9030023
44. Lewis WK, Rosenberger AT, Gord JR, Crouse CA, Harruff BA, *et al*. Multispectroscopic (FTIR, XPS, and TOFMS- TPD) investigation of the core- shell bonding in sonochemically prepared aluminum nanoparticles capped with oleic acid. J Phys Chem C. 2010;114(14):6377-80. doi: 10.1021/jp100274j
45. Zhang L, He R, Gu HC. Oleic acid coating on the monodisperse magnetite nanoparticles. Appl Surf Sci. 2006;253(5):2611-7. doi: 10.1016/j.apsusc.2006.05.023
46. Jagdale SC, Patil SA, Kuchekar BS, Chabukswar AR. Preparation and characterization of Metformin hydrochloride- Compritol 888 ATO solid dispersion. J Young Pharm. 2011;3(3):197-204. doi: 10.4103/0975-1483.83758
47. Tatke A, Dudhipala N, Janga KY, Balguri SP, Avula B, *et al. In situ* gel of triamcinolone acetonide-loaded solid lipid nanoparticles for improved topical ocular delivery: tear kinetics and ocular disposition studies. Nanomaterials. 2018;9(1):33. doi: 10.3390/nano9010033
48. Aburahma MH, Badr-Eldin SM. Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. Expert Opin Drug Deliv. 2014;11(12):1865-83. doi: 10.1517/17425247.2014.935335
49. Tunç S, Duman O, Kancı B. Rheological measurements of Na-bentonite and sepiolite particles in the presence of tetradecyltrimethylammonium bromide, sodium tetradecyl sulfonate and Brij 30 surfactants. Colloids Surf A: Physicochem Eng Asp. 2012;398:37-47. doi: 10.1016/j.colsurfa.2012.02.006
50. Pramod K, Suneesh CV, Shanavas S, Ansari SH, Ali J. Unveiling the compatibility of eugenol with formulation excipients by systematic drug-excipient compatibility studies. J Anal Sci Technol. 2015;6:1-14. doi: 10.1186/s40543-015-0073-2
51. Badria FA, Abdelaziz AE, Hassan AH, Elgazar AA, Mazyed EA. Development of provesicular nanodelivery system of curcumin as a safe and effective antiviral agent: statistical optimization, *in vitro* characterization, and antiviral effectiveness. Molecules. 2020;25(23):5668. doi: 10.3390/molecules25235668
52. Khan Y, Durrani SK, Siddique M, Mehmood M. Hydrothermal synthesis of alpha Fe2O3 nanoparticles capped by Tween-80. Mater Lett. 2011;65(14):2224-7. doi: 10.1016/j.matlet.2011.04.068
53. Agarwal S, Murthy RS, Harikumar SL, Garg R. Quality by design approach for development and characterisation of solid lipid nanoparticles of quetiapine fumarate. Current Computer-Aided Drug Design. 2020;16(1):73-91. doi: 10.2174/1573409915666190722122827

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