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FORMULATION AND EVALUATION OF NABUMETONE LOADED TRANSFERSOMAL GEL

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Keywords:

Nabumetone, Rheumatoid arthritis, Transfersomes, Edge activators

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ABSTRACT: Nabumetone (NBT), a non-steroidal anti-inflammatory drug used to treat rheumatoid arthritis, is rapidly metabolized in the liver and is well known for its side effects along with its sensitivity to light; thus, it limits the formulation of a such drug when considered for skin formulations. Recently introduced a new type of carrier for bioavailability benefits and patient compliance, the "transfersomes". Due to its elastic nature, which can deform and squeeze themselves because of their flexibility through narrow pores of stratum corneum, the transfersomes were prepared by use of phospholipid and sodium cholate, tween 80 as edge activators. The NBT loaded transfersomes were optimized by the three factors and two levels Box-Behnken design using Design-Expert software (version 12). Independent formulation variables such as concentrations of a phospholipid, concentration of sodium cholate, and tween 80 were evaluated. The prepared TFs were evaluated with respect to particle size, % entrapment efficiency, and % drug release. The optimized batch F1 was formulated by incorporation into a Carbopol-940 gel base. The prepared NBT-loaded TFs had particle sizes ranging from 5.32 to 7.65nm, entrapment efficiency in between 33.94 ±0.17% to 73.08 ±0.12%, and drug release 87.94±0.26 to 95.9±0.18%. Thus, transfer-somes, can be explored as a carrier for drug delivery.

INTRODUCTION: Nabumetone is a BCS class II NSAID (Non-Steroidal Anti-Inflammatory Drug). It is mainly used in inflammation by blocking the Cox-2 enzyme. Nabumetone is rapidly metabolized in the liver and forms 6-MNA, the active metabolite that inhibits the cyclooxygenase-2 activity ad that causes pain, fever, and inflammation in the body during arthritis. The topical anti-inflammatory effect for treating rheumatoid arthritis is of major interest because of its fewer side effects than oral therapy. To date, only a tablet formulation of Nabumetone is formulated.

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The purpose of this study was to formulate topical preparation in the form of transferosomal gel, for the treatment of rheumatoid arthritis. Nabumetone possesses high lipid solubility so the drug can pass from stratum corneum by application in the form of topical preparation and use of edge activators as penetration enhancers, it avoids drug loss and produce specific anti-inflammatory effect. Topical delivery system is a localized drug delivery system for local drug delivery through the skin. The advantages of topical delivery are it avoids first pass metabolism, convenient in use and easy to apply, ease of terminate /stop the medication [1].

Transfersomes- (TFs): Transfersomes are artificial vesicles that act as a carrier. They are suitable for controlled drug release because of their cell vesicle engaged in exocytosis. They have extremely flexible and self-regulating membranes which makes them good in deformable **Fig. 1.**

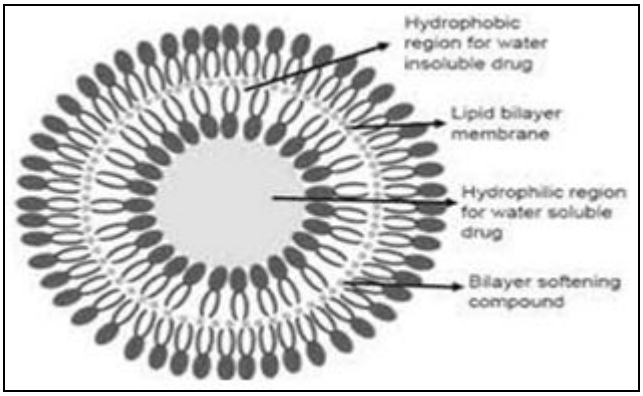

Fig. 1: TRANSFERSOMES STRUCTURE

Advantages:

1. Transfersomes have an internal structure that consists of hydrophobic and hydrophilic moieties together.
2. They are made from natural phospholipid that's why they are bio compatible and biodegradable.
3. They have high entrapment efficiency.
4. Transfersomes have great flexibility because of their squeezing themselves properties.

Disadvantages:

- ❖ Transfersomes formulations are expensive to prepare.
- ❖ Transfersomes are chemically not chemically stable [2, 3, 4, 5, 6].

Mechanism of Transfersomes: There are two mechanisms for enhancing drug delivery across the skin. Transfersomes remain intact, entering throughout the skin as a drug vector. Transfersomes by disrupting the highly organized inter-cellular lipids and act as penetration through the skin [7, 8, 9] **Fig. 2.**

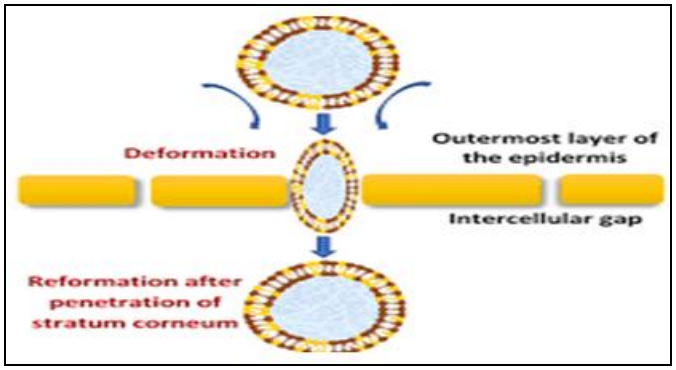

FIG. 2: MECHANISM OF TRANSFERSOMES

MATERIALS AND METHODS:

Materials: The drug Nabumetone was procured from the Cipla Pharmaceuticals Research Centre, Patalganga, Navi Mumbai. Soya-Lecithin powder, Tween 80, and Carbopol-940 these ingredients were available from Analab fine chemicals, Mumbai. Sodium cholate was available from Research-Lab Fine Chem Industries, Mumbai. Polyethylene glycol 4000 and Triethanolamine were provided by Merck Specialties Pvt. Ltd., Mumbai. Methanol and chloroform were available from by Hexon Laboratories Pvt. Ltd., Pune.

Methods:

Preliminary Studies:

Solubility Studies: Solubility studies of NBT in various solvents and different edge activators were carried out. An excess amount of NBT was added to a conical flask containing 5 ml of each solvent and edge activator until equilibrium was achieved. Samples were kept aside at 25^{o}C for constant shaking on an orbital shaker for 45 hours. The resultant solution was filtered through a 0.45 um membrane filter and diluted with a suitable solvent. The concentration of NBT was quantified by UV spectroscopy at 228 nm[10].

Drug-Excipient Compatibility Studies: A Fourier-transform infrared spectroscopy was used for the drug-excipient compatibility study. FTIR of the pure drug NBT and a mixture of the drug with excipients were taken. Infrared spectra were recorded. The peaks of pure drug were compared with the physical mixture of drug and excipients [11].

Differential Scanning Calorimetry (DSC) Studies of Pure Nabumetone: Thermal analysis of pure NBT was performed with Differential Scanning Calorimetry. The DSC thermogram was obtained at a temperature ranging from 30 to 300^{o}C and a scanning rate 10^{o}C/min.[12]

Experimental Design: The Edge activators were screened in preliminary trials. Based on solubility studies, sodium cholate and Tween 80 were selected for the formulation of NBT-loaded TFs because of their flexibility and high lipid permeability features. The nabumetone loaded transfersomes were further optimized by the three factors and two levels box-Behnken design using Design-Expert software (version 12, Stat-Ease Inc.,

and Minneapolis, MN, USA). 3 independent variables were: a) concentration of phospholipid (soya lecithin) b) concentration of sodium cholate c) concentration of Tween 80. A three-factor, two levels Box-Behnken statistical experimental design of the Response Surface Methodology requires 15 runs, of which 12 represent the midpoint of each edge of the multidimensional cube while three are the replicates of the cube's center point. The dependent variables are particle size, percent entrapment efficiency, and percent drug release. The one-way analysis variance (ANOVA) was applied to estimate the significance of the model ($p<0.05$) and individual response parameters in **Tables 1, 2, and 3.**

TABLE 1: INDEPENDENT VARIABLES AND THEIR LEVELS FOR OPTIMIZATION

Independent Variables		Levels	
Concentration of Phospholipid (mg)	X_1	-1	+1
		90	200
Concentration of Sodium cholate (mg)	X_2	30	50
Concentration of Tween 80 (mg)	X_3	10	50

TABLE 2: DEPENDENT VARIABLES SELECTED FOR OPTIMIZATION

Y_1	Particle size (nm)	Response 1
Y_2	Entrapment Efficiency (%)	Response 2
Y_3	Drug release (%)	Response 3

TABLE 3: BOX BEHNKEN DESIGN FOR FORMULATION OF NBT LOADED TFs

Runs	Factor 1(X_1)	Factor 2 (X_2)	Factor 3 (X_3)
F1	200	50	30
F2	145	40	30
F3	90	40	50
F4	145	30	10
F5	145	50	50
F6	200	40	10
F7	90	50	30
F8	145	50	10
F9	200	30	30
F10	90	40	10
F11	145	40	30
F12	90	30	30
F13	145	30	50
F14	200	40	50
F15	145	40	30

Formulation of Nabumetone Loaded Transfersomes: Nabumetone vesicles were prepared by the thin-film hydration method. To prepare a vesicle suspension nabumetone, soya lecithin, edge activators (sodium cholate, Tween 80) were taken in a clean, dry round bottom flask and dissolved in chloroform: methanol (2:1, v/v).

The organic solvent was evaporated in the rotary evaporator under vacuum at 65°C (Popular India) until a thin film formed on the wall of the flask. The deposited lipid film around the wall of RBF was then hydrated with 10 ml of phosphate buffer pH 7.4 by rotation at 60 rpm for 30 min. The resulting vesicles were swollen at room temperature for 1 hr. Later they were sonicated using bath sonicator for 30 min to obtain homogeneous suspension [13].

Preparation of Nabumetone Loaded Transferosomal Gel: Carbopol-940 was dispersed in distilled water. Then the mixture was stirred until it gets thickened. After complete dispersion, 10 ml of propylene glycol was added slowly into the aqueous dispersion of Carbopol-940, and other ingredients, such as 10 ml of isopropyl alcohol and 5 ml of triethanolamine were added. 10 ml of transfersomes dispersion was incorporated into Carbopol gel with continuous stirring. Quantity sufficient distilled water was added to make up the volume up to 100 gm of gel [13].

Characterization of Nabumetone loaded Transfersomes:

Particle Size Analysis: Digital microscope was used to determine the particle size.

The morphological characterization of transfersomes for their shape and surface were obtained by using a digital microscope. Pixel Pro software was used for analyzing the particle size. A drop of transferosome dispersion was placed over the slide. The photomicrographs were taken at 10X resolution, and measurements were conducted in a triplicate manner [14, 15].

% Entrapment Efficiency: Entrapment Efficiency of nabumetone transfersomal vesicles were determined by centrifugation method. Transfersomal suspensions were ultra-centrifuged at 15,000 rpm and 10^{o}C for 30 min. After centrifugation, the supernatant solution was filtered through the membrane. From the filtered solution 1 ml was diluted with the addition of 9 ml phosphate saline buffer (pH 7.4), and then the absorbance was measured using UV–Visible spectrophotometer by measuring absorbance at 228 nm [16]. The % entrapment efficiency was calculated as below:

% Entrapment Efficiency = Total drug- Unentrapped drug / Total drug × 100

***In-vitro* Drug Release Studies:** Vertical Franz diffusion cell was used for evaluating the in vitro drug release. The donor compartment was filled with 1 ml of each formulation and the receptor compartment was filled with phosphate buffer 7.4 up to the mark. The temperature in Franz diffusion cell was maintained at 37± 0.5 ºC, and the receptor compartment was stirred continuously at 50 rpm using a magnetic stirrer.1 ml sample was withdrawn from the receptor compartment, diluted up to 10 ml, and immediately replaced with an equal volume of fresh diffusion medium. Finally, the sample's concentration of nabumetone was analyzed using UV spectrophotometry at 228 nm. Similarly, after every one hour, the sample was withdrawn and was subjected to UV analysis that was done in triplicate manner and mean ±SD was noted. The study was carried out for 4 hours [17].

pH Measurement: The electrode was immersed in the dispersion of transfersomal liquid, and the pH measurement of transfersomes was carried out using digital pH meter [18].

Determination of Particle Size: The particle size of the prepared optimized nabumetone loaded transfersomes batch was measured using a particle analyzer, applying dynamic light scattering techniques. For particle size measurement, Transfersomes fluid was diluted with distilled water. Ultra-sonication was done to prevent agglomeration for 10 minutes. The measurements were performed in triplicate at 25^{o}C under a fixed scattering angle of 173^{o,} and the mean ±SD was calculated [19].

DSC Studies of Optimized Nabumetone Loaded TFs: A thermal analysis of optimized nabumetone loaded transfersomal formulation was performed. DSC was performed to observe any physicochemical interaction between the drug and excipients [19]. Differential thermo analytical technique used for analyzing thermal transitions involving thermal energy with great sensitivity. The nabumetone and mixture of excipients for DSC studies are shown in **Fig. 6** & **7.**

Evaluation of Nabumetone Loaded Transfersomal Gel:

Physical Appearance: The prepared gel was checked visually for identification of its appearance and color.

Homogeneity: The gel was tested for its homogeneity by visual observation. The gel was tested for the presence of any aggregates

Spreadability: The Spreadability of gel formulation was determined by placing 1 gm of gel between horizontal plates for 1 min by putting a specific weight at one side. Spreadability was measured by measuring the diameter of gel spread over 1 min [20].

pH Measurement: pH measurement of optimized Nabumetone loaded transfersomal gel was carried out using digital pH meter [20].

Viscosity: A Brookfield Programmable DV-II + Viscometer was used to measure gel formulation's viscosity (in cps). The spindle was rotated at 5, 10, 20 50 100 rpm/min, and the sample were allowed to settle over 30 minutes at the temperature 25^{o}C before the measurements were taken [21].

***In-vitro* Drug Release:** The *In-vitro* drug release of gel was performed using a vertical Franz diffusion cell. The same procedure is followed, described earlier while carrying out In-vitro drug release of

the TFs. The difference is only 1 gm of gel was placed in the donor compartment and the study was carried out for 8 hours [21]. The *in-vitro* drug release profile is shown in **Fig. 14.**

Stability Study: For the stability study, TFs solution and optimized Nabumetone loaded transfersomal gel was stored at 25°C/60% RH for long-term stability, 40°C/ 75% RH for accelerated stability, and 5±3°C in refrigerator condition. Stability studies were carried out for three months [22, 23].

RESULTS AND DISCUSSION:

Preformulation Parameter of Drug:

Physical Appearance: Nabumetone was checked visually for its color, odor, and nature, and the results are mentioned in **Table 4.**

TABLE 4: PHYSICAL APPEARANCE OF NBT

Sr. no.	Physicochemical properties	Observation
1	Color	White to off white
2	Odor	Odorless
3	Appearance	Crystalline powder
4	Solubility	In ethanol

Melting Point: The melting point of Nabumetone was found to be 78°C- 82°C.

Screening of Edge Activators: The Solubility studies of Nabumetone in different edge activators were determined by the shake flask method. The edge activators having the highest solubility were selected for optimization and formulation of transfersomes given in **Fig. 3.**

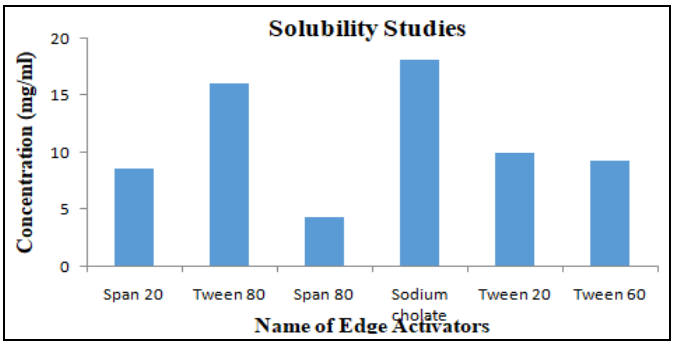

FIG. 3: SOLUBILITY STUDIES OF NABUMETONE IN DIFFERENT EDGE ACTIVATORS

Transfersomes have highly efficient edge activators based on ultra-flexible vesicles, so the selection of proper edge activators plays an important role in the formulation process. Nabumetone was found to be more soluble in Tween 80 and Sodium cholate; hence they were selected for formulation (The type of edge activator and its concentration affects on the vesicle size, % entrapment efficiency, and % drug release). Therefore, by using a combination of two surfactants at different concentrations was selected for optimization and formulation of TFs.[24]

Drug-Excipient Compatibility Studies Drug-Excipient Compatibility studies were performed using Fourier Transform Infrared Spectroscopy (FTIR). The results are given in **Table 5.**

TABLE 5: FTIR OF NBT

Functional group	Observed peak
C-H Stretching	2970-2850
C=O Stretching	1750-1705
Ether O-CH3	2850-2815
C=C=C aromatic ring stretching	1680-1620

No alteration in the IR values of the physical mixture was observed, indicating compatibility in drug and excipients.

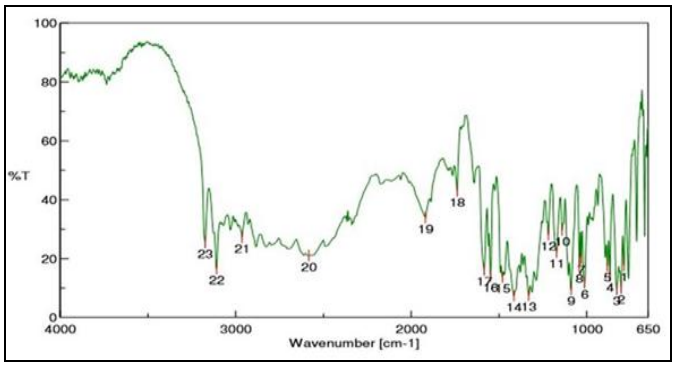

FIG. 4: FTIR SPECTRA OF NBT

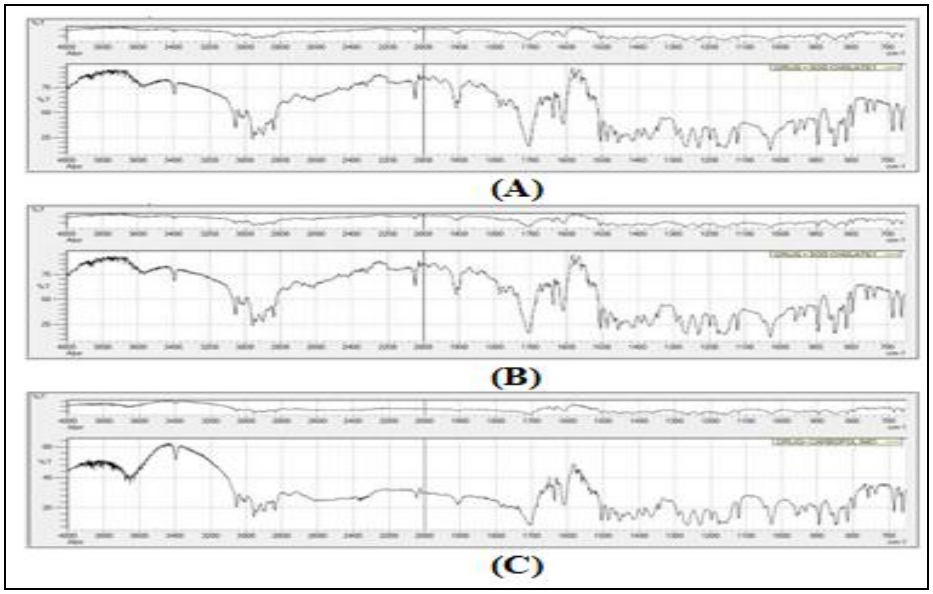

FIG. 5: FTIR SPECTRA (A) NBT + SOYA LECITHIN (B) NBT + SODIUM CHOLATE (C) NBT +PHYSICAL MIXTURE OF EXCIPIENTS

DSC of Pure Drug and Physical Mixture: A differential thermoanalytical technique used for analyzing thermal transitions involving thermal energy with great sensitivity. From the DSC analyses drug alone elicited a peak at 81.91^{o}C very close to the reported value of Nabumetone melting point. Nabumetone with a mixture of excipients at 100.1oC was found to have characteristic features of Nabumetone. These two peaks are close to each other. Thus, it indicated no physical interaction between Nabumetone and excipients, as shown in **Fig. 6 & 7.**

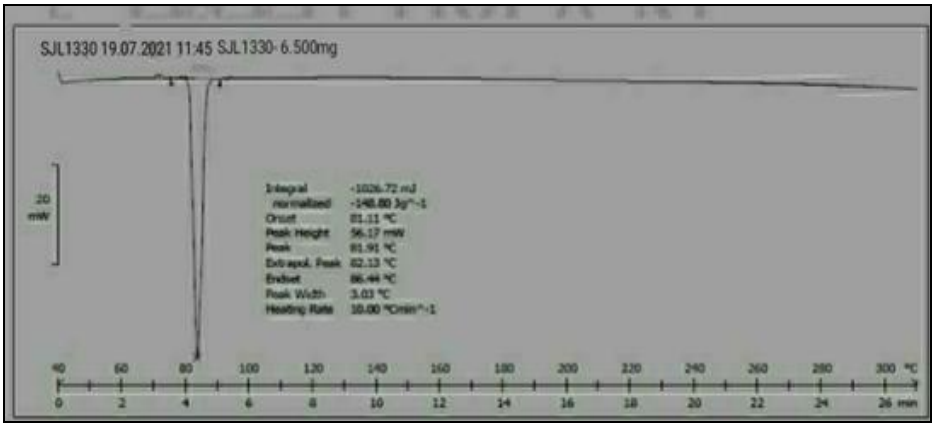

FIG. 6: DSC OF NBT

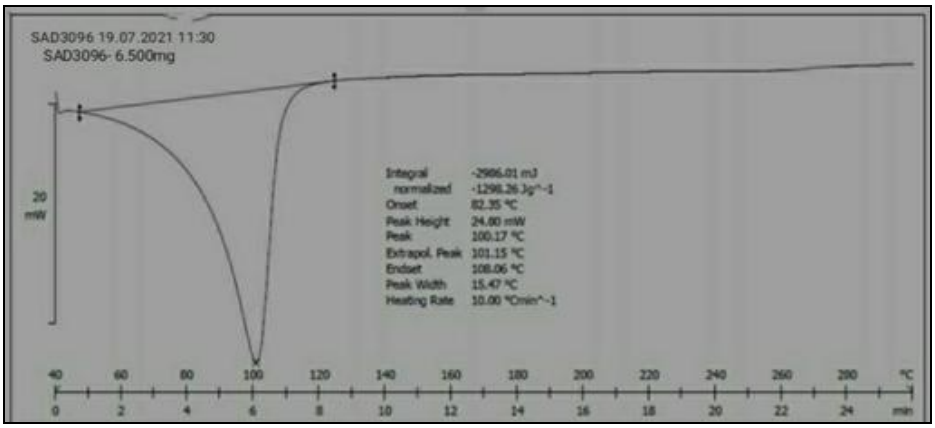

FIG. 7: DSC OF NBT WITH PHYSICAL MIXTURE OF EXCIPIENTS

Particle size:

Effect of Phospholipid Concentration of Phospholipid and Concentration of Edge Activators on Particle Size: A is the concentration of phospholipid, B is the concentration of sodium cholate, and C is the concentration of Tween 80. It was seen that the particle size was significantly affected by variables A, B, and C. Concentration of phospholipid had a positive effect on the particle size in **Fig. 8** & **9**. It was seen that the particle size increased with an increase in the phospholipid concentration significantly. The largest particle size was observed in the concentration of positive one level of A, while the small particle size was observed in the negative one level of A. It might be due to the increase in phospholipid concentration; more phospholipids molecules will be distributed in the lipid bilayer, causing an increase in the transfersomes mean diameter or due to the insufficient drug molecules for a complete degree of association with the phospholipids.

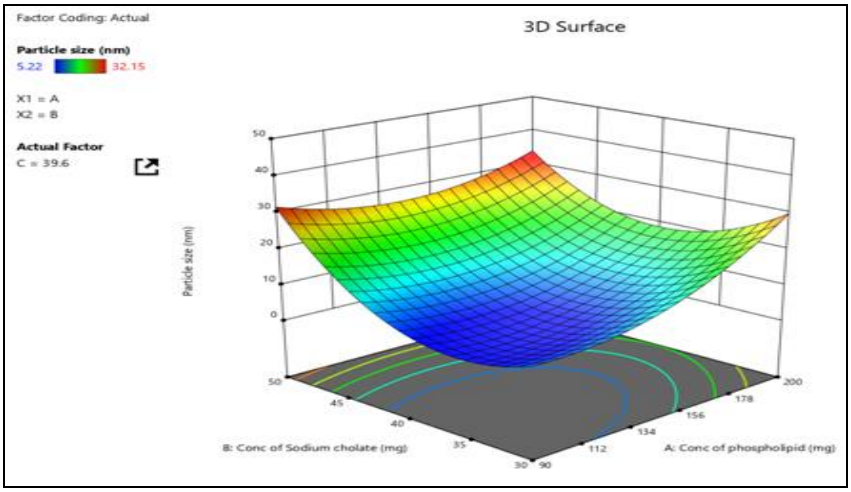

FIG. 8: 3D PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF SURFACTANT ON PARTICLE SIZE

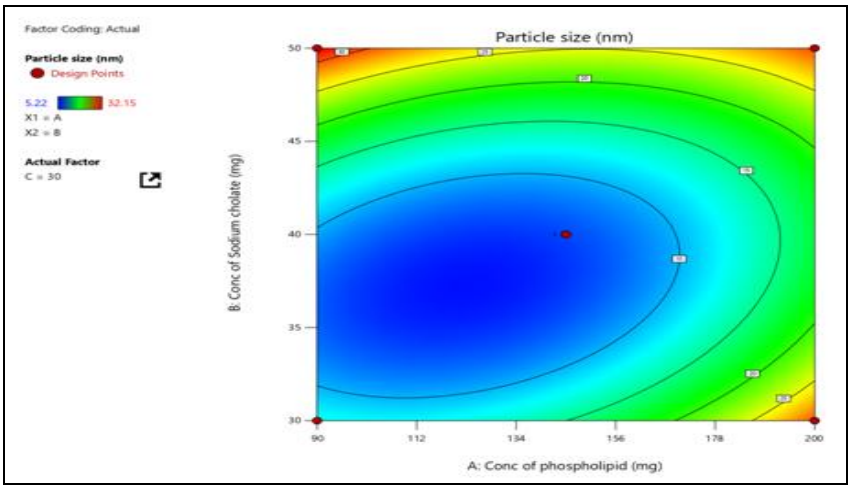

FIG. 9: CONTOUR PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF EDGE ACTIVATORS ON PARTICLE SIZE

It was observed that the particle size decreased with an increase in the sodium cholate concentration. It might be due to the higher concentration of edge activator allowing better stabilization of the smaller lipid vesicles and preventing aggregation into larger droplets [25]. Here, on particle size, tween 80 showed a positive effect with the presence of sodium cholate, *i.e.,* Tween 80 on its negative level. The particle size was increased while smaller particle size on its positive level. ANOVA Table & R^2 for particle size shown in **Tables 6** & **7.**

Final Equation in Terms of Coded Factors. Y_1 (particle size) = 7.52+307A+5.12B-353C 4.94AB+4.74AC+3.81BC+6.06A^2+12.77B2+5.07 C^2.

TABLE 6: ANOVA FOR RESPONSE SURFACE (PARTICLE SIZE)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**1417.15**	**9**	**157.46**	**23.64**	**0.0014**	**significant**
A- Conc of phospholipid	113.18	1	113.18	16.99	0.0092	
B-Conc of sod cholate	209.61	1	209.61	31.46	0.0025	
C-Conc of tween 80	99.41	1	99.41	14.92	0.0118	
AB	97.71	1	97.71	14.67	0.0123	
AC	89.68	1	89.68	13.46	0.0145	
BC	58.06	1	58.06	8.72	0.0318	
A^2	135.39	1	135.39	20.32	0.0064	
B^2	602.15	1	602.15	90.39	0.0002	
C^2	94.83	1	94.83	14.23	0.0130	

TABLE 7: R^2 RESPONSE OF PARTICLE SIZE

Std. Dev.	2.58	R^2	0.9770
Mean	20.26	Adjusted R^2	0.9357
C.V. %	12.74	Predicted R^2	0.8048
		Adeq Precision	12.3484

***In-vitro* Drug Release Studies:**

Effect of Concentration of Phospholipids and Concentration of Edge Activators on % Drug Release: The drug release was between 79.61±0.21 to 89.1±0.11 %. Results in **Fig. 10** & **11** showed that the phospholipid concentration had the opposite effect on drug release. This may be due to the higher the phospholipid concentration, the harder the vesicular structure formed, which tightly entrapped the drug molecule in the structure and hindered the drug release into the dissolution media [26].

% Drug Release =+33.67+8.32A-153B-3.72C+6.48AB+4.61AC-6.03BC+17.52A^2-2.66B^2+14.48C^2

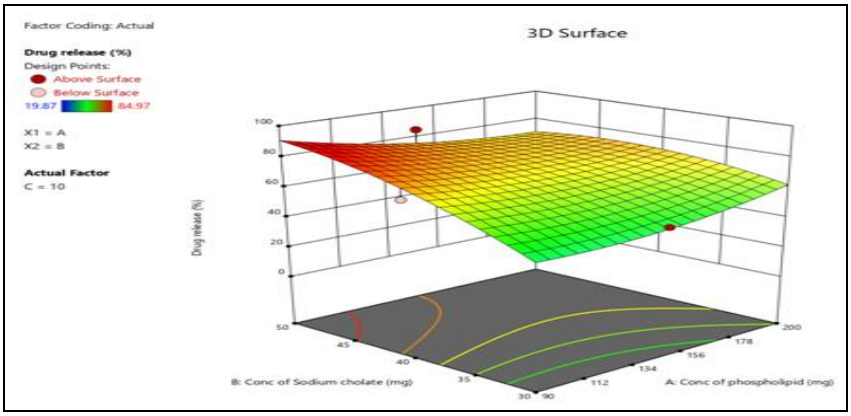

FIG. 10: 3D PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF EDGE ACTIVATORS ON DRUG RELEASE

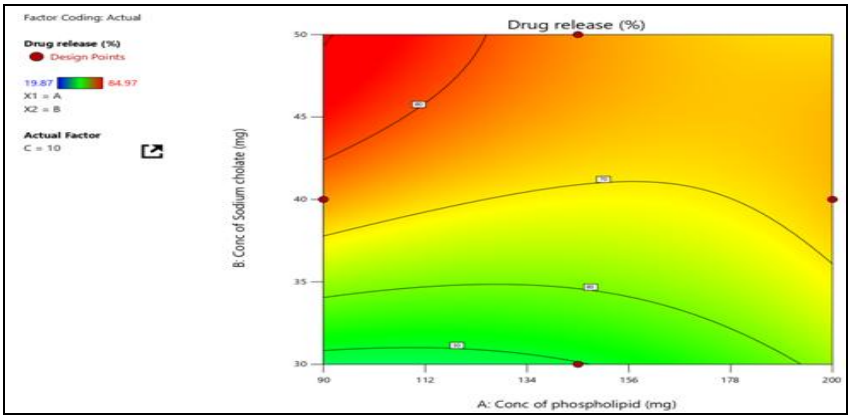

FIG. 11: CONTOUR PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF EDGE ACTIVATORS ON DRUG RELEASE

It was observed that an increase in sodium cholate concentration increased the drug release. The sodium cholate concentration at a positive level (60 mg) showed 89.9±0.28% drug release. This is due to the increase in edge activator concentration, which increased the hydrophilicity of the vesicles, thereby promoting drug release into the dissolution medium. It was seen that edge activators' concentrations synergistically affected the percent drug release. ANOVA Table & R^2 for drug release is shown in **Tables 8** & **9.**

TABLE 8: ANOVA FOR RESPONSE SURFACE DRUG RELEASE

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3701.92	9	411.32	43.78	0.0003	significant
A-conc of phospholipid	91.80	1	91.80	9.77	0.0261	
B-Conc of sod cholate	333.59	1	333.59	35.51	0.0019	
C-Conc of tween 80	110.86	1	110.86	11.80	0.0185	
AB	301.02	1	301.02	32.04	0.0024	
AC	85.19	1	85.19	9.07	0.0297	
BC	145.68	1	145.68	15.51	0.0110	
A^2	365.06	1	365.06	38.85	0.0016	
B^2	386.91	1	386.91	41.18	0.0014	
C^2	1795.75	1	1795.75	191.13	< 0.0001	

TABLE 9: R^2 RESPONSE FOR DRUG RELEASE

Std. Dev.	3.07	**R^2**	0.9875
Mean	45.28	Adjusted R^2	0.9649
C.V. %	6.77	Predicted R^2	0.8098
		Adeq Precision	19.5727

Entrapment Efficiency:

Effect of Concentration of Phospholipids and Concentration of Edge activators on % Entrapment Efficiency: The entrapment efficiency of all formulated transfersomes was found in the range 33.94 ±0.17% to 73.08 ±0.12%. The entrapment efficiency was directly proportional to the phospholipid concentration due to the phospholipids acting as solubilizing agents for highly lipophilic drugs. It was observed that entrapment efficiency increased with an increase in sodium cholate concentration mentioned in **Fig. 12** & **13.** The entrapment efficiency in transfersomes dispersion increased due to the incorporation of the edge activator sodium cholate inside the structure of vesicles. Another reason is sodium cholate is a salt of bile acids of a steroidal amphiphilic chemical structure that can form micelles consisting of 2-12 monomer units [27]. It was clearly seen that the Tween 80 positively affected entrapment efficiency. And it shows a negative level of sodium cholate concentration. For this reason, entrapment efficiency was seen only when Tween 80 or sodium cholate concentration was used in formulation on their opposite levels. ANOVA Table and R^2 for entrapment efficiency are shown in **Tables 10** & **11.**

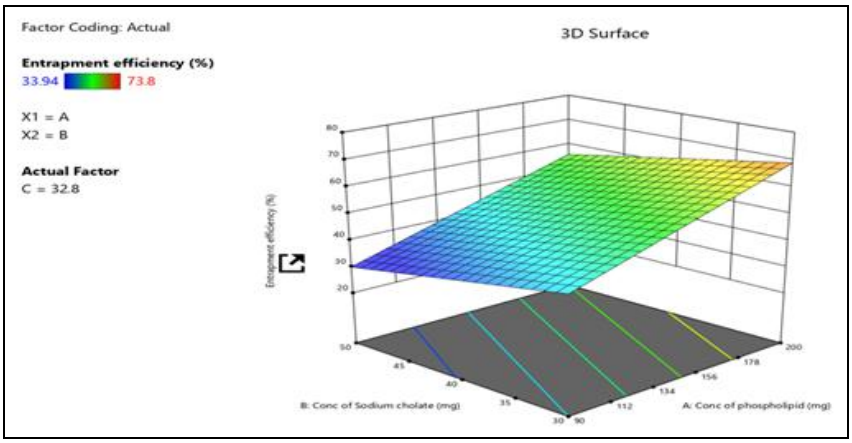

FIG. 12: 3D PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF EDGE ACTIVATORS ON ENTRAPMENT EFFICIENCY

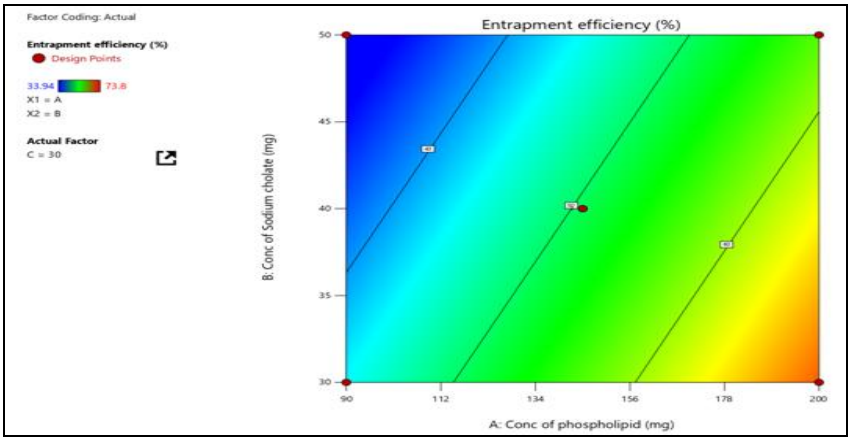

FIG. 13: CONTOUR PLOT FOR EFFECT OF CONCENTRATION OF LIPIDS AND CONCENTRATION OF EDGE ACTIVATORS ON ENTRAPMENT EFFICIENCY

TABLE 10: ANOVA FOR ENTRAPMENT EFFICIENCY

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2154.62	3	718.21	47.44	< 0.0001	significant
A-conc of phospholipid	1326.90	1	1326.90	87.65	< 0.0001	
B-Conc of sod cholate	323.85	1	323.85	21.39	0.0007	
C-Conc of tween 80	503.87	1	503.87	33.28	0.0001	
Residual	166.52	11	15.14			
Lack of Fit	133.20	9	14.80	0.8883	0.6339	Not significant
Pure Error	33.32	2	16.66			
Cor Total	2321.15	14				

TABLE 11: R^2 RESPONSE FOR ENTRAPMENT EFFICIENCY

Std. Dev.	3.89	R^2	0.9283
Mean	51.02	Adjusted R^2	0.9087
C.V. %	7.63	Predicted R^2	0.8681
		Adeq Precision	20.7195

Stability Study: The stability studies were studied over different storage conditions of 5°C and 25°C as per ICH guidelines. Both physical and chemical changes were studied for 3 months. Physical stability was checked based on the appearance and particle size of formulated drug, whereas chemical studies were checked based on entrapment efficiency and drug release profile. The results showed no significant change in particle size, entrapment efficiency, and drug release of the SLN formulation stored at 5°C and 25°C after 3 months. The results for stability of optimized Nabumetone loaded TFs, and its prepared gel is shown in **Tables 12 & 13.**

TABLE 12: STABILITY STUDY OF OPTIMIZED NABUMETONE LOADED TRANSFERSOMES

Months	Visual examination	pH	Spreadability gm.cm/sec	*In-vitro* drug release (%)
Initial	Transparent, Smooth, Homogenous	6.7±0.02	6.80 ± 0.2	95.04±0.80%
First month	Transparent, Smooth, Homogenous	6.7±0.01	6.78±0.3	94.89±0.56%
Second month	Transparent, Smooth, Homogenous	6.7±0.03	6.58±02	92.76±0.78%
After third month	Transparent, Smooth, Homogenous	6.7±0.03	6.45± 0.2	91.41±0.5%

Values are expressed as mean ± S.D. (n = 3)

TABLE 13: STABILITY STUDIES OF OPTIMIZED NABUMETONE LADED TRANSFERSOMAL GEL

Months	Temperature Condition (^oC)	Optimized NBT Loaded Transfersomal Gel	
		Spreadability gm.cm/sec	% Drug Release (%)
1	5±3^{o}C	5.99±0.11	95.90±0.07
	25^{o}C/60% RH	6.00±0.14	96.30±0.05
2	5±3^{o}C	5.78±0.09	94.89±0.08

	25°C/60% RH	5.81±0.12	96.02±0.04
3	5±3°C	5.75±0.18	94.68±0.11
	25°C/60% RH	5.85±0.09	95.05±0.08

Values are expressed as mean ± S.D. (n = 3)

Evaluation of Topical Gel:

Homogeneity: The developed gel was tested for homogeneity by visual observation, and the gel was found to be homogenous.

Physical Evaluation: Physical parameters were tested for color, appearance, and odor. F1 batch was evaluated by physical inspection, and the results are given in **Table 14.**

TABLE 14: PHYSICAL EVALUATION OF OPTIMIZED GEL

Sr. no.	Parameter	Observations
1	Appearance	Smooth
2	Odor	Pleasant
3	Color	Transparent white
4	pH	6.7±0.02
5	Spreadability	6.80 ± 0.2 gm.cm/sec

Values are expressed as mean ± S.D. (n = 3)

Viscosity Study: The viscosity of the gel at different r.p.m was stated. The viscosity was found to decrease with the increase in the r.p.m. *i.e*., the shear rate showed with the non-Newtonian flow. This behavior might be due to its low flow resistance when applied at high shear conditions. The results showed that in **Table 15**, as the concentration of Carbopol 940 increased from 0.2 % to 0.5 %, the viscosity was increased as the r.p.m. increased there was a decrease in viscosity.

TABLE 15: THE VISCOSITY OF OPTIMIZED GEL

Sr. no.	RPM	Viscosity (Centipoise)
1	5	2665±0.3
2	10	2571±0.2
3	20	2531±0.1
4	50	2399±0.5
5	100	2314±0.1

Values are expressed as mean ± S.D. (n = 3)

Spreadability: Spreadability is important for patient compliance, and it also helps in the uniform application of the gel to the skin. A good gel spreads easily and quickly spread on the skin. The spreadability of the optimized gel was found to be 6.45± 0.2 gm.cm/min.

CONCLUSION: In this present work, nabumetone loaded transfersomes were successfully formulated by the thin-film hydration method. The three factors and two levels box-Behnken design optimized the formulations using Design-Expert software. Results proved that particle size, percent entrapment efficiency, and percent drug release were mainly affected by the concentration of phospholipid and concentrations of edge activators in the formulations. This study concluded that the Box-Behnken design could obtain an optimized formula of nabumetone-loaded transfersomes, with small particle size, high percent entrapment efficiency, and percent drug release.

The F1 batch of NBT-loaded TFs formulation was found to be optimized with a particle size of 5.32-7.65nm, percent entrapment efficiency of 72.8±0.18%, and percent drug release 91.41±0.5. Nabumetone Transfersomes may be used as alternative carriers for transdermal drug delivery systems because Nabumetone-loaded transfersomal gel could overcome the skin's barrier properties.

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