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Formulation and Development of Niosomes Loaded Hydrogel to Treat Rheumatoid Arthritis

Patel Jatin R.*, Dr. Ujashkumar Shah[1], Dr. Anar J. Patel[2]

*Research Scholar, Nootan Pharmacy College, Sankalchand Patel University, Visnagar, Gujarat, India.

[1]Nootan Pharmacy College, Sankalchand Patel University, Visnagar, Gujarat, India.

[2]Kalol Institute of Pharmacy, Kalol, Ghandhinagar, Gujarat, India.

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KEYWORDS

Flurbiprofen, Niosomes, Rheumatoid Arthritis, Quality by Design Approach, 3^2 Factorial design

ABSTRACT:

Introduction: Niosomal vesicles are a soluble matrix that can be used as a rate-limiting membrane barrier to alter systemic drug absorption by dermal drug delivery, as a local repository for medications that must be released gradually, or as a permeation enhancer for dermally active substances. Niosomes have attracted attention due to their chemical resistance, high reliability, material consistency, low cost, ease of storage of nonionic surfactants, and the availability of surfactants for their production. Flurbiprofen, a BCS class II medication with low solubility (8 mg/L) and high permeability (Log P = 3.80), is seen to be a good option for niosome formulation in order to address issues including short half-life, limited bioavailability, and stomach side effects.

Objectives: To Control/ modify release of drug at specific site and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy. To Show better in-vitro release/ diffusion performance than conventional dosage forms.

Methods: Flurbiprofen loaded niosomes were prepared using the Ether Injection method, and the main effect, interaction effects, and quadratic effects were evaluated using 3^2 FFD (Quality by Design) using Design Expert Software (VR 10.0.1). Span 60 (X1) and cholesterol (X2) were chosen as independent variables with low, medium, and high values to maximize the niosomes. Particle size (Y1) and Entrapment Efficacy (Y2) were the dependent variables.

Results: Flurbiprofen Niosomes loaded hydrogel were having 94.25±1.32 CDR in 10 hrs which clearly indicates better in vitro release/diffusion than conventional dosage form as well as shows better patient compliance. Also, it indicates controlled release pattern at specific site in reduced dose frequency.

1. Introduction

Because niosome targets the infection site, improves skin penetration and deposition, and minimizes side effects by avoiding systemic absorption, topical medication delivered via vesicles is a common option for treating superficial and cutaneous infections. Reasonably designed drug delivery systems can release drugs at a predetermined rate and timing, which helps to increase medicine efficacy by getting around current limitations. Indeed, by enhancing topical drug distribution, nonionic surfactant vesicles, or niosomes, have demonstrated the ability to increase the permeability and bioavailability of medications that are weakly water soluble. They also hold promise for enhancing the NSAIDs activity. Because of their extended biological system circulation, niosomes facilitate the absorption of encapsulated drugs at the intended location and reduce drug toxicity by minimize non-specific tissue uptake.

Flurbiprofen is a derivative of phenyl alkanoic acid, a nonsteroidal anti-inflammatory drug (NSAID) related to ibuprofen in structure. The commercial dosage forms of flurbiprofen are tablets, sustained release capsules, and

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eye drops. It is used in the treatment of gout, rheumatoid arthritis, osteoarthritis, and other rheumatic disorders. Administration of flurbiprofen via the skin could have benefits over oral administration, since it is a non-invasive administration (convenient and safe) and is suitable to people who can't use the oral route due to vomiting or unconsciousness. Also, topical route eliminates first pass metabolism and the GI side effects of the drug.

Additionally, it can increase patient compliance and decrease the frequency of administration. Therefore, flurbiprofen, a BCS class II medication with low solubility (8 mg/L) and high permeability (Log P = 3.80), is seen to be a good option for niosome formulation in order to address issues including short half-life, limited bioavailability, and stomach side effects.

Formulation and Development of API Niosomalgel by using QbD Approach

STEP- I: Quality Target product Profile (QTPP)

Formulation of API Loaded Niosomes:

The API was first dissolve in an organic phase (diethyl ether and methanol), till entire drug was dissolve. In a 20 mL glass scintillation vial, Span 60, cholesterol, and lipid will be added to the solution and stirred using a magnetic spin bar. Purified water will be heated 60°C temperatures in a separate 50 mL glass beaker using a hot plate with magnetic stirring. The temperature of the water phase will be chosen to meet the design criteria. A 14G needle was used to fill the organic phase into a 10 mL syringe. Using predefined settings based on the experimental design, the organic phase mixture was injected into the preheated aqueous phase. The values discovered from the design of experiment will be used to mix the ingredients (DoE). The batch was cooled to room temperature in the final step of the process, and the formulation will be kept in a suitable glass storage container. [1-2]

Setting up Quality Target Product Profile (QTPP) and Selection of Formulation and Process Variables by Preliminary Trial Batches of API Niosomes [3]

Design Expert 10.0.1 was employed for optimization in this case. The factorial design was utilized to determine the key process variables in this investigation. A look at the consequences of eight different variables. The following tests were performed: surfactant concentration, cholesterol concentration, lipid concentration, organic phase composition, organic phase volume, aqueous volume, stirring speed, and stirring time. Based on a thorough assessment of the literature and preliminary trials, the high and low levels for independent variables were chosen. Sonication was used to prepare niosomes. For technique optimization, factorial designs were employed to look for critical elements that affect the development of niosomes. This strategy enables the identification of the impacts of a large number of factors in a small and manageable number of experiments. As a result, these designs were particularly beneficial in preliminary investigations aimed at identifying formulation variables that could be changed or eliminated. [3, 4]

Selection of Stirring Time

The Niosomal gel will be formulated using constant RPM speed at different stirring time i.e., 30 Min, and 60 Min while other variables will be constant and the formed Niosomal gel will be evaluated.

STEP-II: Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach

Risk Assessment of Critical Quality Attributes (CQAs) from Preliminary trial Batches to Develop QbD Approach

Initial risk assessment studies were undertaken to identify potential elements that could have a greater impact on the final product's quality than others. Critical material attributes (MAs) and process parameters (PPs) were chosen as a result. The Ishikawa fish-bone diagram was created to identify distinct risk factors that can contribute to product failure in order to determine the cause-effect relationship. The risk estimation matrix was used to priorities the components based on the level of risk on the formulation process based on the risk assessment (RM). CMAs and CPPs were selected using RM based on the low, medium, and high-risk potential of each of the components. The screening of criteria to consider for undertaking optimization studies was then done. [3, 4]

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STEP-III: Formulation and Development of API Niosomes by Design of Experiment (DoE) Using QbD Approach

Formulation and Development of Flurbiprofen Niosomes by using QbD Approach

The Flurbiprofen loaded niosomes were prepared using the Ether Injection method, and the main effect, interaction effects, and quadratic effects were evaluated using 3^2 FFD by Design Expert (VR 10.0.1). Span 60 (X1) and cholesterol (X2) were chosen as independent variables with low, medium, and high values to maximize the niosomes. Particle size (Y1) and Entrapment Efficacy (Y2) were the dependent variables. According to research, cholesterol levels and Span 60 were all shown to have a significant impact on the size and entrapment efficacy, and were so chosen as independent variables. [3, 4]

2. Characterization of API Niosome [5, 6]:
Particle size and zeta potential measurements

The particle size distribution of API loaded niosomes were examined at 25°C using the Malvern Zeta sizer. The niosomal dispersion was diluted with twice distilled water and vortexed for 1 minute before each measurement. The particle electrophoretic mobility measurements collected in distilled water will be used to assess the zeta potential of vesicles. Triplicates of each measurement were taken.

Entrapment Efficiency

The material was centrifuged at 8000 rpm for 1 hour at 5 C using a cooling centrifuge to measure the encapsulation efficiency of API loaded niosomes. After dilution with mobile phase, the unentrapped API in the supernatant was separated and quantified using a devised UV technique at 247 nm. [7, 8]

It was calculated by following formula: -

$$\%\text{Drug Encapsulation efficiency} = \frac{\text{Total amount of Drug Content - Free amount of Drug}}{\text{Total amount of Drug}} \times 100$$

3. *In Vitro* Drug Release Study of Niosomes

In a USP-I Type dissolving equipment, the dissolution test was performed in 900 mL Phosphate buffer (PH 7.4) at 37.5 °C, 150 RPM. Every hour for up to 8 hours, aliquots were removed and refilled with fresh solvent. Using a UV-visible spectrophotometer, the sample's absorbance at max 247 nm was calculated. Also, figure out the percent CDR. [9]

Preparation and Characterization of API Niosomal gel

Method of Preparation API Niosomal gel

Niosomes aqueous dispersion were utilized for the formulation of topical gel. Gel polymer such as carbopol-934 were utilized to make niosome gel. 1g of carbopol-934 powder were dispersed into forcefully mixed and allowed to hydrate for 24 hrs. Following that, 10 mL of propylene glycol was added. The dispersion was neutralized with the drop wise addition of 10 percent Triethanolamine, mixing wer continued until a translucent gel will be emerged. [10, 11]

Preliminary Trial batches of API Niosomal gel

Preliminary trials were undertaken to develop API loaded Niosomal gel. The various concentrations of Carbopol 934P was taken. [10]

Characterization of API Niosomal gel

Physical Appearance

It was done to evaluate organoleptic property, Occlusiveness and washability of gel.

Measurement of pH

The pH of the niosomal gel formulation was measured using a digital pH metre. 5 mg API niosomal gel was dispersed evenly in 5 mL distilled water and stored for 2 hours at room temperature. At 25 °C, the pH of the dispersion was determined. [12]

Viscosity study

5 gm of prepared gel was kept in 50 mL suitable beaker and spindle Groove was dipped at specific RPM in Brookfield Viscometer. This was done for three times and from the recorded observation mean was calculated. [13]

Spreadability study

A glass plate containing 1 g of niosomal gel was placed on top of it, and another glass plate was dropped into it from a distance of 5 cm. [14]

Spreadability will be determined using the equation:

$$S = ML/T$$

Where, S is the Spreadability,
M is the weight tied to the upper side,
L is the length of the glass slide and
T is the time taken to separate the slide from each other.

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Homogeneity and grittiness

By pressing the produced gel between the thumb and index finger, the consistency was determined. A small amount of gel will be applied to the back of the hand to check for homogeneity and grittiness. [15]

Drug content:

In a volumetric flask, 1 gramme of each gel formulation was dissolved in 20 mL of alcohol after 30 minutes of stirring. It will be then diluted and filtered. A further dilution to 10 mL alcohol were made, and 1 mL was removed from the above and diluted to 10 mL alcohol once more. In ultraviolet light, the absorbance was measure at 247 nm. [16]

In vitro diffusion study:

A modified Franz diffusion cell was used in the in-vitro drug release tests (With effective diffusion area 2.54 cm^2 and 20 ml cell volume). The formulation will be applied to a dialysis membrane interposed between the donor and receptor compartments of the Franz diffusion cell (which had previously been soaked in Phosphate buffer pH 7.4 for 24 hours). As a dissolving medium, phosphate buffer pH 7.4 was utilised. The cell will be kept in a water bath to maintain a temperature of 37.0± 2°C. This entire assembly was placed on a magnetic stirrer, and the solution was continually stirred at 50rpm using a magnetic bead. After proper dilutions, the samples (1ml aliquots) were extracted at appropriate time intervals and tested for drug content using a UV visible spectrophotometer at 247 nm. [15, 16]

Results

Design of Experiment 10.0.1. Was used for Statistical assessment and made first solicitation polynomial circumstances. From major results, 3^2 full factorial design was utilized in which two factors were surveyed, freely at three levels and possible nine mixes were sorted out. Three level factorial assessments were finished using two novel elements. In first factorial arrangement, proportion of Cholesterol (X1) and Span 60 (X2) were taken as independent elements while Particle Size (Y1), % Entrapment Efficiency (%) (Y2) were picked as dependent elements for both factorial plans.

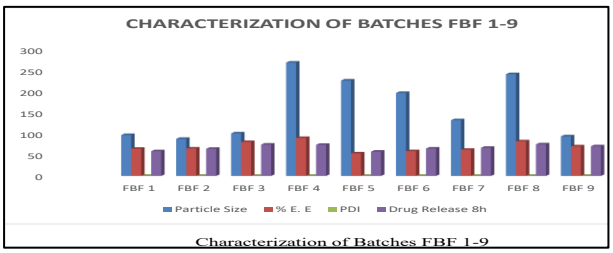
3^2 Factorial Design Approach

Table: 3^2Factorial Batches			
Independent variables of formulations			
Independent variables (X1)	Low (-1)	Medium (0)	High (+1)
Cholesterol (mg)	5	10	15
Span 60 (mg)	10	15	20
Dependent variables			
Y1= Particle Size			
Y2= Entrapment Efficiency			

Compositions of Factorial Batches in Decoded Form

Table: Compositions of Factorial Batches in Decoded Form as per Design Expert

BATCH CODE	RUNS	Vol. of Cholesterol (mg) (X1)	Vol. of Span 60 (mg) (X2)	P.S. (nm) (Y1)	%E.E (%) (Y2)
3^2 FFD		X-Variables Responses		Y-Variables Responses	
FBF 1	1	10	20	97.24	64.63
FBF 2	2	10	15	88.15	65.25
FBF 3	3	5	20	101.1	80.66
FBF 4	4	5	10	269.1	90.21
FBF 5	5	15	20	226.7	53.61
FBF 6	6	15	15	197.1	58.87
FBF 7	7	15	10	132.3	62.15
FBF 8	8	5	15	241.76	82.25
FBF 9	9	10	10	94.14	70.36



Effect on Particle Size (Y1) - Surface Response Study:

The results of multiple linear regression analysis showed that both the coefficients β1and β2 bear a positive sign. Therefore, increasing the concentration of either cholesterol or span 60 is expected to increase the particle size. The result of analysis of Variance for Y1 (particle size) was shown in Table, that indicates the quadratic model was found an adequate model. The three-dimensional response surface plot was shown in Figure and Contour plot Figure indicates the effect of cholesterol and span 60 on the particle size of niosomes.

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P.S = +107.99 - 9.31 * A - 11.76 * B + 65.58 * AB +101.541 * A^2 - 22.22 * B^2

Table: Result of Analysis of Variance for Y1 (Particle Size)						
ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	40166.51	5	8033.30	12.53	0.0318	significant
A-Chl Conc.	520.24	1	520.24	0.81	0.4342	
B-Span 60 Conc.	830.02	1	830.02	1.29	0.3379	
AB	17205.57	1	17205.57	26.83	0.0140	
A^2	20622.77	1	20622.77	32.15	0.0109	
B^2	987.90	1	987.90	1.54	0.3028	
Residual	1924.14	3	641.38			
Cor Total	42090.65	8				

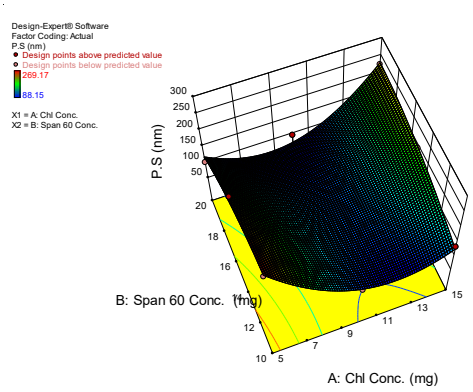

Figure: Response surface plot illustrating the influence of Cholesterol and Span 60 on the particle size

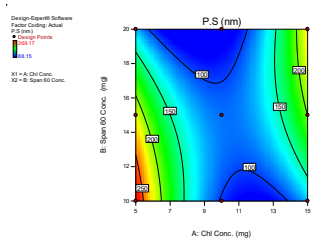

Figure: Contour plot illustrating the influence of Cholesterol and Span 60 on the particle size of niosomes

Effect on Entrapment Efficiency (Y2) - Surface Response Study:

The after effects of numerous direct relapse investigation showed that both the coefficients β1 and β2 bear a negative sign. Accordingly, expanding the grouping of one or the other Cholesterol or Span 60 is supposed to diminish the capture productivity. Three-layered reaction surface plot and Two-layered shape plot were displayed in Figure 8 and Figure 9, show the impact of cholesterol and range 60 on the capture proficiency of niosomes. With expanding in the centralization of cholesterol and range 60 were found to impact or diminish the entanglement proficiency of the arranged niosomes. Graphical portrayal of entanglement proficiency and molecule size is given in Figure.

Y2 (%E.E) = +65.76 - 13.0816 * A - 3.970 * B + 0.25 * AB + 4.545* A^2 + 1.48* B^2

Table: Result of Analysis of Variance for Y2 (Entrapment Efficiency)						
ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	1167.30	5	233.46	69.63	0.0027	significant
A-Chl Conc.	1026.78	1	1026.78	306.24	0.0004	
B-Span 60 Conc.	94.57	1	94.57	28.20	0.0130	
AB	0.26	1	0.26	0.076	0.8006	
A^2	41.31	1	41.31	12.32	0.0392	
B^2	4.38	1	4.38	1.31	0.3360	
Residual	10.06	3	3.35			
Cor Total	1177.35	8				

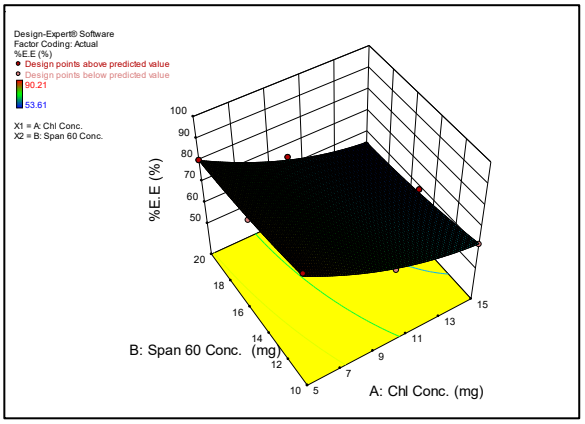

Figure: Response surface plot illustrating the influence of Cholesterol and Span 60 on the Entrapment efficiency

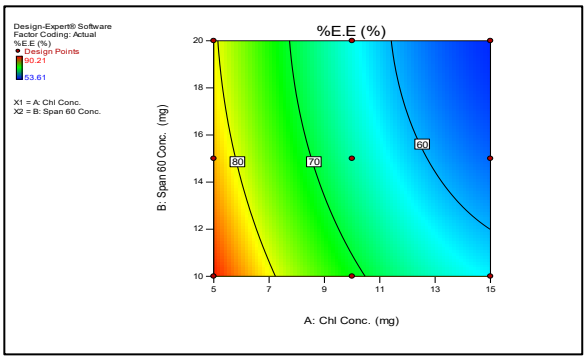

Figure: Contour plot illustrating the influence of Cholesterol and Span 60 on the Entrapment efficiency

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Validation of Model:

Validation or check point analysis were done by formulation and characterization of predicted batches from Overlay plots suggested by Design Expert software. The predicted and observed batches results were compared.

Tab. 1: Validation of Model

Check point batches	Independent Variables		Response variables	Predicted value	Observed value
	X1: Cholesterol (mg)	X2: Span 60 (mg)			
C1	5	20	Y1 (nm)	119.275	118.5 nm
			Y2 (%)	80.64 %	82.21%

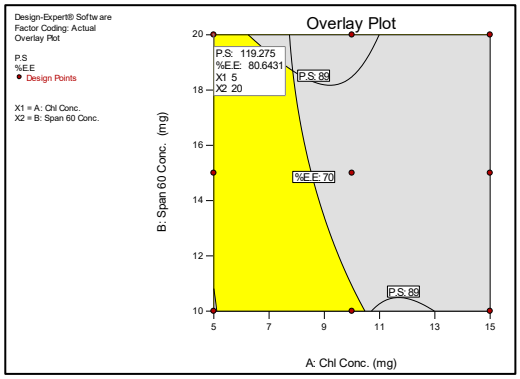

Fig. 1: Overlay plot 1

% Cumulative Drug Release profile

Tab. 1: % CDR profile

Time (hr)	C1
0	0
1	09.18±1.53
2	18.38±1.66
3	25.63±1.48
4	38.47±1.21
5	49.75±1.35
6	62.38±1.69
7	71.20±1.42
8	82.21±1.29

Preliminary Trial batches of Topical gel

Tab. 2: Formulation Design of Topical Gel trial Batches

Ingredient	1	2	3	4
Carbopol (%w/v)	0.5	1	1.5	2.0
PG (mL)	5	5	5	5
MP	0.1	0.1	0.1	0.1
PP	0.05	0.05	0.05	0.05
Triethanolamine(mL)	0.25	0.25	0.25	0.25
Water(mL)	100	100	100	100

Tab. 3: Result of Evaluation of gel

Batch code	Colour	Odour	pH (Mean ± S.D.) (n = 3)	Viscosity Spindleno:62 (Mean ± S.D.) (n = 3)	Spreadability (gm.cm/sec) (Mean ± S.D.) (n = 3)
1	Cream white	Odourless	6.6 ± 0.01	9180 ± 62	9.21 ± 0.95
2	Cream white	Odourless	6.4 ± 0.07	9426 ± 21	9.38 ± 1.34
3	Cream white	Odourless	6.2 ± 0.02	11340 ± 05	9.33 ± 1.51
4	Cream white	Odourless	6.3 ± 0.03	11483 ± 77	9.46 ± 1.38

Characterization of topical gel

Tab. 4: Result of Optimised Topical Gel

Parameters	Optimized Niosomal Gel
Dose	608 mg Niosomes
Strength	10 gm
Clarity	Cream white
Odour	Odourless
pH (Mean ± S.D.) (n = 3)	6.6 ± 0.01
Spreadability (Mean ± S.D.) (n = 3)	9.21 ± 0.95
Viscosity (Mean ± S.D.) (n = 3)	9180 ± 62cps
% Drug content (Mean ± S.D.) (n = 3)	90.02±0.90

Dose Calculation of Flurbiprofen Niosomes for Topical Gel:

Dose Calculation for Loading Flurbiprofen Niosomes into Topical Gel:

10 gm of marketed Flurbiprofen Gel (Brugel) contains 5% Flurbiprofen as drug

10 gm of gel = 10 gm Flurbiprofen i.e. 100% Flurbiprofen as Drug.

500 * 100/82.21 = 608.19 mg Flurbiprofen Niosomes required.

In vitro Release study of Flurbiprofen Niosomal gel

Tab. 5: In-Vitro drug release study

Time (hr)	Optimized Niosomal Gel (Mean ± S.D.) (n=3)	Conventional marketed formulation (Mean ± S.D.) (n=3)
0	0	0
1	7.42±1.62	19.18±1.72
2	15.65±1.51	33.31±1.89
3	24.07±1.07	49.67±1.53
4	37.73±1.08	67.40±1.35
5	45.11±1.53	82.75±1.79
6	56.78±1.78	95.38±1.85
7	63.55±1.23	-
8	75.12±1.16	-
9	85.69±1.47	
10	94.25±1.32	

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Release Kinetic

Tab. 6: Release Kinetic of Flurbiprofen Niosomal gel.

Model	Parameter	Optimized Gel
Zero Order	**R2**	0.9564
	Slop	8.121
	Intercept	12.27
First Order	**R2**	0.9636
	Slop	0.147
	Intercept	4.49
Higuchi Model	**R2**	0.9736
	Slop	26.93
	Intercept	1.79
Hixon Crowell	**R2**	0.8417
	Slop	0.86
	Intercept	2.38
Korsmeyer Peppas	**R2**	0.4359
	Slop	0.53
	Intercept	-0.66

By plotting the qualities for Higuchi model, close to straight lines with equal positive inclines were acquired showing that, the best fit model for the details was Higuchi model.

Stability Analysis

Tab. 7: Stability Analysis of C1 at Room Temperature for 1 Months

PARAMETER	Optimized Flurbiprofen Niosomes loaded Gel			
	Room Temperature			
	0 Day	10 Day	20 Day	30 Day
Clarity	Transparent	Transparent	Transparent	Transparent
Colour	Cream White	Cream White	Cream White	Cream White
Odour	Odourless	Odourless	Odourless	Odourless
pH	6.6	6.56	6.56	6.53
Spreadability	9.21	9.20	9.20	9.18
Viscosity	9180	9178	9177	9176
% Drug content	90.02	89.91	93.60	93.60
%CDR	94.25±1.32	94.20±1.56	93.90±1.02	93.78±1.14

Conclusion

The Current research work aims to form non-ionic surfactant niosomal vesicles for topical application of Flurbiprofen for use in Rheumatoid. The aim was reducing dose and dose frequency and decrease the oral side effects like gastritis, ulcers and so on which is made possible with the development of niosomal hydrogel of flurbiprofen. It improves drug bioavailability, in vitro performance/diffusion as well as gives better patient compliance. With its enhanced anti-inflammatory impact (Anti Rheumatoid Arthritis) and controlled medication release over the skin, this gel may prove to be an effective carrier.

Conflict of Interest: The authors affirm that no financial or business ties that may be interpreted as a possible conflict of interest existed at the time the research was carried out.

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Ethics approval and consent to participate: None.

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