

Preparation and Evaluation of a Sustained Release Niosomal Dispersion Containing Niflumic Acid

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ABSTRACT

Objective: This work aims to create and characterize niosomal dispersions for long-term delivery of the anti-inflammatory drug niflumic acid that may be adapted to give a localized effect, prevent gastrointestinal side effects and hepatic metabolism, leading to improve efficacy and patient compliance.

Method: The thin film hydration technique was used to make niflumic acid-loaded niosomes. The effects of different concentrations of a non-ionic surfactant, cholesterol, dicetyl phosphate (DCP), sonication time and the effects of drug concentration on encapsulation efficiency were investigated in order to improve the process. Differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR), and transmission electron microscopy (TEM) were used to analyze the formulations. The niosomal dispersion formulations were evaluated for entrapment efficiency, in-vitro drug release, particle size, polydispersity index (pdI), zeta potential, pH and stability study.

Results: The optimum niosomal preparation (F15) exhibited pH (7.2), size of the particles (1.04 µm), pdI (0.374), surface charge (-47.4) and efficiency of trapping (91.55%). It gave a rapid release in 15 minutes and increased sustainably over time until reach 96.9% within 24 hours.

Conclusion: This research was successful in producing an optimal niosomal dispersion for niflumic acid using different surfactant/cholesterol ratios. The optimum formula provides a sustained release with the initial fast effect of niflumic acid and can be used with a topical dosage form to provide immediate relief that lasts for up to 24 h.

Keywords: Cholesterol, Dicetyl Phosphate, Niosome, Niflumic acid, Span, Tween.

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INTRODUCTION

Niosomes are novel delivery systems, in which drug is incorporated into a vesicle. Niosomes are self-assembled vesicles mainly composed of synthetic surfactants and cholesterol in aqueous media. They are bilayers of non-ionic surfactant vesicles. Niosomal vesicles act as a rate-controlling membrane that regulates systemic drug absorption. Because the vesicles can act as drug reservoirs, drug delivery via niosomal vesicles has a number of advantages over traditional dosage forms.¹ Niosomal vesicles and their components showed a great effect on solubility of drugs and increased transdermal absorption of lipophilic and hydrophilic drugs.²

Niosomes have a unique structure that allows them to encapsulate both hydrophilic and lipophilic medicinal molecules. The capacity of niosomes as a medication carrier has been intensively researched in recent years. They have a long shelf life and allow the drug to be delivered to the target

site in a controlled and/or sustained manner.³ Niosomes can be delivered via intramuscular, intravenous, intraperitoneal, pulmonary, subcutaneous, ophthalmic, topical, oral, and transdermal routes, depending on their size and structure. They're also biocompatible, biodegradable, non-immunogenic, and have a low toxicity level.⁴ Furthermore, due of their particle size and surface composition, include these vesicles in gel matrices improves drug uptake and reduces skin irritation.⁵ Niflumic acid is a non-steroidal anti-inflammatory drug, it has analgesic, antipyretic, and platelet-inhibitory actions and is used to cure rheumatoid arthritis and acute pain.⁶ Niflumic acid is classified under the BCS (Biopharmaceutical Classification System) as Class II category, which means it has poor aqueous solubility and high permeability.⁷

The goal of this research is to make niosomal dispersion for niflumic acid to improve drug solubility and to give sustained release profile to deliver the drug to the required site, reducing

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Table 1: Composition and condition of niosomal dispersion formulas

Formulation codes	Surfactants used	Niflumic acid: surfactant: cholesterol (molar ratio)	Dicetyl phosphate (DCP) (mg)	Sonication time
F1	Tween 80	1:1:1	-	-
F2	Tween 80	1:1:1.5	-	-
F3	Tween 80	1:1:0.5	-	-
F4	Tween 80	1:0.5:1	-	-
F5	Tween 80	1:1.5:1	-	-
F6	Tween 60	1:1:1	-	-
F7	Span 60	1:1:1	-	-
F8	Span 40	1:1:1	-	-
F9	Tween 80	1:1:1	-	2.5 min
F10	Tween 80	1:1:1	-	5 min
F11	Tween 80	1:1:1	-	10 min
F12	Tween 80	1:1:1	-	15 min
F13	Tween 80	1:1:1	1mg	2.5 min
F14	Tween 80	1:1:1	2mg	2.5 min
F15	Tween 80	1:1:1	4mg	2.5 min

side effect and local irritation leading to improved patient compliance.

MATERIALS AND METHODS MATERIALS

Niflumic acid (NFA), Cholesterol and Dicetyl Phosphate (DCP) were obtained from (Hangzhou Hyper chemicals, China). Chloroform and methanol from (Chem-lab, Belgium), Himedia provided the dialysis membrane. Sigma-Aldrich provided the Tween 60, Tween 80, Span 40, and Span 60.

Preparation for Niosomal Dispersion

Thin film hydration techniques were used to prepare niosomal dispersions and studied the effects of using various types of surfactants (tween 80, tween 60, span 60, span 40) and cholesterol, as well as different drugs: surface active agent: cholesterol ratio, in addition to the sonication time as shown in Table 1.

To keep the niosomes stable for a long time and demonstrate its effect on entrapment efficiency, different concentrations of DCP were added to the formulation. In 10mL chloroform : methanol (1:1), then weighted quantities of each surfactant and cholesterol (in a specific ratio) were dissolved in a flask with round bottom then DCP was mixed with the above mixture along with an precisely weighed amount of drug, and the solvent was evaporated under vacuum in a rotary evaporator flask at 60°C until a smooth, dry lipid film was obtained.. The film was then hydrated for 1-hours at 60 ± 2°C using water bath with shaking in 10 mL PBS 7. 4. Some of the niosomal preparations were sonicated using probe sonicator and stored at 2–8°C for 24 hours.⁸

Calculation of Entrapment Efficiency

The centrifugation method was used to determine the entrapment efficiency of niosomal dispersion formulas (F1-F15). 10 mL of preparation was placed in a stopper test tube and spun at 15,000 rpm for 60 minutes at 4°C using a cooling centrifuge to produce a fraction that is clear. Using a UV spectrophotometer set to 287 nm, the clear fraction was used to determine the free drug.⁹ The entrapment efficiency was calculated using the following equation.¹⁰

$$\text{Entrapment Efficiency (\%)} = [(Ct - Cf)/Ct \times 100]$$

where Ct is concentration of total drug and Cf is concentration of unentrapped drug.

Variables Affecting the Entrapment Efficiency of the Prepared Niosomal Dispersion

Effects of Different Types of Surfactants

Different types of surfactants (tween 80, tween 60, span 40 and span 60) were used to prepare F1, F6, F7, F8 respectively keeping the same ratio of 1:1:1 niflumic acid: surfactant : cholesterol without DCP and no sonication in order to study the effect of surfactant type on niosomal entrapment efficiency.¹¹

Effect of Different Amounts of Surfactant

To demonstrate the influence of surfactant ratio on EE percent, three formulations were created with varied ratios or percentages of Tween 80, F1 (33.3%), F4 (20%), and F5 (42.8%), while maintaining the same niflumic acid:cholesterol ratio (1:1) without DCP and sonication.¹²

Effects of Different Amounts of Cholesterol

The impact of cholesterol ratio on EE% was determined in F1, F2, F3 which were formulated to contain different amount of cholesterol using same niflumic acid: tween 80 ratio (1:1), without DCP and no sonication.¹³

Effect of Different Sonication Times

The effect of sonication time on EE% were investigated in F9, F10, F11 and F12 which were prepared with 2, 5, 5, 10 and 15 minutes of sonication using a probe sonicator (30% of the 150W power), keeping same ratio of niflumic acid: cholesterol: surfactant ratio 1:1:1 without adding DCP in comparison to F1 (prepared without sonication).¹⁴

Effects of Different Amounts of Dicetylphosphate

F13, F14 and F15 formulas were prepared containing 1, 2 and 4 mg DCP keeping the same niflumic acid: tween80: cholesterol ratio 1:1:1 and 2. 5 minutes sonication time in comparison to F9 (prepared without DCP).¹⁵

Characterization of the Prepared Niosomal Dispersions

Physical Appearance, Homogeneity and Clarity

Visual observations were used to determine the physical appearance, homogeneity, and purity of the prepared niosomal dispersions (F1-F15) after they had been placed in a clear container and the presence of any aggregates was tested.¹⁶

pH Measurements

The pH of all niosomal dispersion formulas (F1-F15) was recorded with the aid of pH meter. Before measurement, the

pH meter was calibrated and the glass rod was dipped in the dispersions to get readings.¹⁷

In-vitro Release Studies

The dialysis bag methods used to conduct in vitro release studies of niosome dispersion (F1, F9, F10, F11, F12, and F15). The dialysis sac was thoroughly cleansed and immersed in distilled water. After sealing one end with a clip, 2 mL of each niosomal dispersion was poured onto the dialysis tubing and the bag was secured with another closure clip to prevent leaking. A beaker containing 200 mL of PBS 7.4 was used to place the dialysis bag. The temperature in the beaker was kept at 37°C by placing it over a magnetic stirrer (100 rpm). Fresh buffer was added to 10 mL samples that had been removed from the medium at regular intervals of 1 hours for 10 h and then after 15 hours, 20 hours and at the end of 24 hours. Using a UV/visible spectrophotometer set at 287 nm, samples were diluted and drug content was determined.¹⁸

The Shape of the Vesicle

A transmission electron microscopy (TEM) instrument was used to investigate the vesicle shapes of niosomal dispersion preparations (F1, F9, and F15). Deionized water was used to dilute the niosomal dispersion ten times. A drop of diluted niosomal dispersion was applied to a carbon-coated 300 mesh copper grid and left for 1 minute to permit some of the niosomes to stick to the carbon substrate. By absorbing the drop with the corner of a sheet of filter paper, the leftover dispersion was eliminated. After repeatedly washing the grid with deionized water for 3–5 seconds, a drop of 2% aqueous uranyl acetate solution was applied for 1sec. The remainder of the solution was absorbed with the tip of a slice of filter paper, and the sample was air dried.¹⁹

Determination of Surface Charge, Size of a Particle, and Polydispersity Index

Using DLC, the size of particle (mean diameter), particle surface charge (zeta potential), and size range of particles (polydispersity index) for the preparations formulas (F1, F9, and F15) were determined (ZetaPlus ParticleSizing). This technique was used to investigate light scattering variations, which are caused by the Brownian motion of niosomal dispersion particles. At room temperature, one mL of diluted niosomal suspension was injected into a folded capillary zeta cell and light scattering was monitored.²⁰

Selection of the Best Formula

The optimal formula was chosen based on its highest entrapment efficiency, drug release profile, particle size, zeta potential, good vesicle shape, pH, and acceptable physical appearance.

Stability Study

The best niosomal dispersion formula (F15) was kept in tightly sealed vials and stored in two separate storage conditions, room temperature and refrigerator temperature, for a period of 30 days, according to the ICH guidelines. For a month, the efficiency of entrapment and in vitro release were re-evaluated once a week.^{21,22}

Table 2: Entrapment efficiencies of the prepared niosomal formulas.

Formulation codes	Entrapment efficiency (%)
F1	87.44 ± 1.84
F2	82.64 ± 1.89
F3	81.49 ± 1.91
F4	85.39 ± 1.76
F5	82.04 ± 2.66
F6	82.1 ± 2
F7	80.22 ± 0.79
F8	82.58±1.04
F9	80.16 ± 1.71
F10	78.12 ± 2.13
F11	77.5 ± 2.02
F12	77.21 ± 1.42
F13	82.73 ± 0.42
F14	87.85 ± 0.53
F15	91.55 ± 1.61

*Average of three determination

RESULT AND DISCUSSION

The Entrapment Efficiency of the Prepared Niosomal Dispersion

Entrapment efficiency for all the prepared niosomal formulas was determined and the result is shown in Table 2.

Many variables included in the preparation method had different effects on the entrapment efficiency of the drug including:

Effect of Different Type of Surfactants

Entrapment efficiency of niosomal dispersion was affected by type of surfactant used. It was noticed that (F1) formula (containing tween 80 as surfactant) produced higher EE% when compared to niosomes in F6, F7 and F8 formulas (containing Tween 60, span 60 and span 40 respectively) knowing that these formulas containing the same concentration of each surfactant. This is due to the longer unsaturated side chain oleate part of tween 80 that could enhance the packing ability of the poorly water-soluble drug niflumic acid in niosome bilayers. Same results observed with Curcumin niosomes, which showed higher EE% upon using tween 80 as a surfactant.²³

Effect of Different Amount of Surfactant

Changing the amount of surface-active agent had an effect on niosome entrapment efficiency. It was noticed that as the amount of tween 80 increased from 20 to 33. 3% in F4 and F1 respectively, there was increase in entrapment efficiency since the leakage of drug was decreased but upon further increase in tween 80 to 42. 8% in F5, The efficacy of entrapment reduced, which could be attributable to the amount of active ingredient to be encapsulated. which depends on the ability of the drug

to be disposed on the polar and non-polar part of the lipid molecule that forms the vesicle and its ability to diffuse into the vesicles during hydration. Same results observed with niosomes of Aqueous Extract of Cassava Leaves.²⁴

Effect of Different Amount of Cholesterol

The amount of cholesterol was another factor that influenced the entrapment efficiency of niosomal dispersion. When the cholesterol ratio was increased from 0.5 to 1 in F3 and F1, the entrapment efficiency increased, whereas when the cholesterol ratio was increased to 1.5 in F2, the entrapment efficiency decreased. This could be explained by the fact that as the cholesterol ratio increased (from 0.5 to 1), bilayer vesicles became more stable and hydrophobic, while permeability decreased. As the vesicles form, this could result in the hydrophobic drug being trapped efficiently in bilayers, but the larger cholesterol amount may compete with the drug for packing space within the bilayer, thus excluding the drug. Same results observed with niosomes of clarithromycin.²⁵

Effect of Different Sonication Time

Sonication time also influence entrapment efficiency of noisome, when sonication time increase from 2.5 to 5, 10 and 15 minutes in formula F9, F10, F11 and F12, entrapment efficiency slightly decreased because sonication causes homogenous distribution of the drug leading to uniform entrapment of the drug within the vesicles but upon further increase in sonication time leaching of the drug from the prepared vesicles might happen leading to lower EE in F11 and F12. Similar results observed with niosomes of ibuprofen, where EE% first increased, then it decreased upon further increased in sonication time.²⁶

Effect of Different Amount of DCP

The entrapment efficiency of niosomal dispersion was also affected by different amounts of the charge-inducing agent (DCP). When concentration of DCP, increased in F13 (containing 1mg DCP), F14 (with 2 mg DCP) and F15 (with 4 mg DCP), the entrapment efficiency increased without any aggregations. This is because the lipid layer contains a charge inducing agent that prevents vesicles from aggregating and fusing, preserving their integrity and uniformity. Same results observed with



Figure 2 : Physical appearance of niosomal dispersion of niflumic acid.

niosomes of zidovudine, when the optimal concentration of DCP was added, spherical vesicles with enhanced drug entrapment and no aggregation were formed.²⁷

Physical Appearance, Homogeneity and Clarity

As shown in Figure 3, all of niosomal preparations (F1-F15) appeared as a milky homogeneous solution with no aggregates. This finding suggests that the thin film hydration technique is an effective method for preparing niosomal dispersion. Same results observed with niosomes of dexamethasone.¹⁶

pH Determination

The pH of the niosomal dispersion formulas (F1-F15) was determined using a pH meter. The pH values ranged from 6.43 to 7.32, The pH ranged from 6.43 to 7.32, which was consistent with adapalene results obtained using a topical niosomal gel and met the standards for topical skin treatments to avoid irritation.²⁸

In-vitro Release Studies

From the results of variables and characterization, formulas F1, F9, F10, F11, F12, F13, F14 and F15 were chosen to study their in vitro release and investigate the effect of different variables on the release profile of the drug.

The choice based on the following:

Formula F1 having high E. E with 1:1:1 niflumic acid: surfactant: cholesterol molar ratio. Formulas F9, F10, F11 and F12 formulas having the same content of F1, only differ in their sonication time, while Formulas F13 and F14 having same content and conditions of F15 except containing different amount of DCP. In addition to that, F15 having highest E. E with same content of F1 except sonication and DCP.

The in-vitro release studies for F1, F9, F10, F11, F12, F13, F14 and F15 were carried out by diffusion method and the percent of drug released are shown in Table 2 and Figure 4.

In-vitro drug release of niflumic acid from niosomal dispersion is biphasic, with an early release phase followed by a continuous release for 24 hours, according to the findings. The same was said about some liposomes and niosomes.²⁹

The initial drug release with the first hour (T 1-hours) was not significantly different for F1, F9, F10, F11, F12, F13, F14 and F15 formulas (15, 16, 3, 16, 15, 14, 13, 5, 12, 43 and 11. 54% release respectively), This early drug release could be attributed to the release of adsorbed drug from the lipophilic region of niosomes.²⁷ After 10 hours (T 10 hours) the drug release increased gradually from all formulations (F1, F9, F10, F11, F12, F13, F14 and F15) until reach 83, 79, 89, 88, 72, 82, 8, 82 and 80% respectively and continued to increase to reach 97, 97, 19, 95, 7, 93, 57, 80, 81, 94, 92, 32 and 90. 65% respectively after 24 hours (T 24 hours).

F12 formula showed a significantly ($p < 0.05$) lower release profile than other formula because it has lowest E. E that could be due to prolonged sonication (15 min) that caused leakage of the drug from the prepared niosomes.¹⁰

F15 formula (containing 4 mg DCP and sonication time 2.5 min) exhibit lower drug release than F1 formula (without DCP and sonication) at all time because charge inducing agent (DCP) causes holding the release efficacy due to it has

the ability to stabilize the niosomal membrane structure and render it less permeable. The molecular packaging of the vesicle bilayers is also tightened by charged lipids, resulting in slow release from charged niosomal membranes. The same outcome was found with tenoxicam niosomes.³⁰

The efficacy of sonication time is observed on the release of the drug formulas F9, F10, F11 and F12 that had the same content but prepared with 2. 5,5,10 and 15 min sonication time, respectively, it was observed that F12 formula (15 mins sonication) showed significant lower drug release than F9 (2. 5 min), F10 (5 mins) and F11 (10 mins) and the order of drug release was F12<F11<F10<F9. So as the sonication time increased, the drug release decreased because excessive sonication time lead to a decrease E. E that leads to increase leakage of drug from prepared niosomes. Same results observed with Pilocarpine hydrochloride prepared as niosomes.³¹

F13 (containing 1 mg DCP) and F14 (containing 2 mg DCP) formulas exhibit lower release than F15 formula (containing 4 mg DCP) at all times of drug release. The results indicated that as the amount of DCP increased, the drug release decreased and these results agreed with the highest drug release observed with formula F1(containing no DCP) due to tightening effect of DCP. The Same results obtained with niosomes of hepatoprotective drug silymarin.³²

On the basis of the above result, it was found that F1, F9, F15 each one had distinct results; thus, they were selected for further investigation.

Vesicle Shape

Transmission electron microscopy (TEM) for the selected formulas (F1,F9, F15) was carried out. The spherical shape and morphology of the niosomes were revealed in a TEM photomicrograph of (F1, F9, and F15) niosomal formulation. Furthermore, niosomes were discovered to have a hollow vesicular structure. Same morphology observed with niosomes of cefdinir.³³

Determination of Surface Chage, Size of Particle, and Polydispersity Index

measurement of particle size, PDI and zeta potential are shown in Table 3 and Figure 4 and 5. All niosomal dispersions (F1, F9, and F15) had an effective diameters within micrometer range (average particle size values ranged from 1. 04 μ m to

Table 3: %Cumulative drug release from the prepared niosomal dispersions

Formulation code	%Drug release at 1-hours	%Drug release at 10 hours	%Drug release at 24 hours
F1	15	83	97.01
F9	16.3	79	97.19
F10	16	89	95.7
F11	15	88	93.87
F12	14	72	80.81
F13	13.5	82.8	94
F14	12.43	82	92.32
F15	11.54	80	90.65

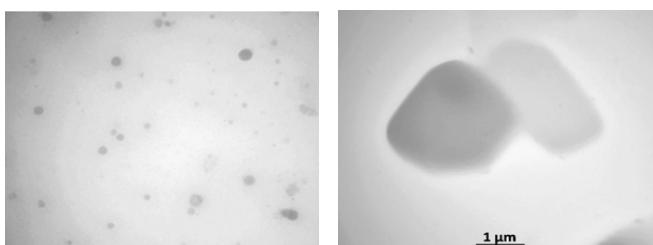


Figure 1: Transmission electron microscopy of selected niosomal dispersion (F15)

1. 78 μ m), with a polydispersity index of < 1, low value of polydispersity index 0. 08-0. 7 is considered to be desirable for uniform distribution and homogeneity of the particles within the preparation. Particle size distribution is seen to be broad when the pdI value is more than 0. 7 but less than 1(108). F1 formula show larger particle size than F9 and F15 because it is not subjected to sonication process since sonication leads to reduce aggregates and particle size to produce homogenous dispersion, same results observed with niosomes of sorbitan monopalmitate. 34 Formula F15 showed smaller particle size than F9 and F10 (both were sonicated for 2. 5 min) due to the presence of DCP in F15 which act as charge-inducing agent that stabilize the dispersion and minimized the aggregation behavior, Same result obsereveed with niosomes of 5-fluorouracil.³⁵

The zeta potential of all formulas (F1, F9 and F15) are good, ranging between (-33. 69 to -47. 40 mV). F15 formula exhibit better zeta potential (-47. 40 mV) than F1 and F9 (-33. 69 mV and 34. 46 mV), respectively which could be due to the presence of charge-inducing agent (DCP) in niosomal ingredients, DCP is a common charge inducer additive that imparts a negative charge on the surface of niosomes, preventing vesicle aggregation and fusion while maintaining vesicle integrity and uniformity.³⁶ Thus, the inclusion of DCP in niosomes (F15) enhanced the zeta potential compared to formulations containing tween 80 without DCP (F1 and F9). The zeta potential influence on particle stability was explained using thumb rule. According to this rule, values of zeta potential in the range of (-30mV) to (+30mV) indicate good stability, while values in the range of (-60mV) to (+60mV) indicate excellent stability in the formulation.

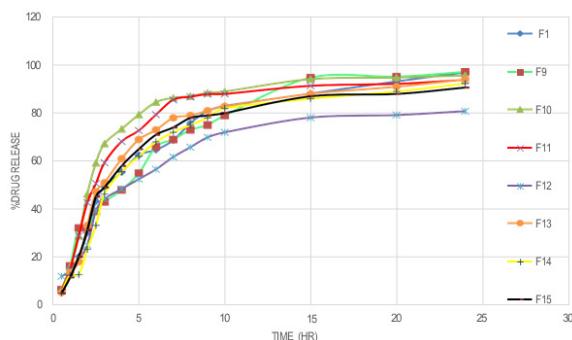
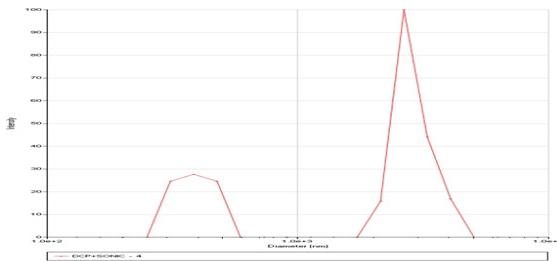


Figure 3: Release profile of niflumic acid for the prepared niosomal dispersion

Table 4: PdI, ζ -potential and effective diameter, of prepared niosomal dispersion formulas.

Formulation code	ζ - potential (mV)	Effective diameter in (μm)	Observed pdI
F1(no sonication + no DCP)	-33.69	1.78	0.701
F9(no DCP + sonication)	-34.46	1.30	0.407
F15 (DCP + sonication)	-47.4	1.04	0.374

**Figure 4:** Particle size distribution of the selected formula (F15)

Selection of the Best Formula

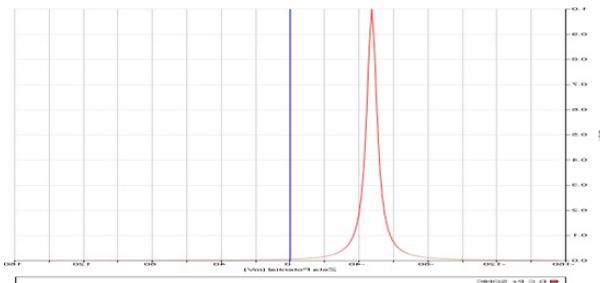
F15 was selected as the optimum formula because it has highest EE% (91. 55%), high in-vitro drug release within 24 hours (90. 65%), smallest particle size (1. 04 μm) which is suitable to be incorporated in topical preparation, optimum zeta potential (-47. 4 mV), homogenous appearance and acceptable pH measurement (7. 32). Therefore, it could be suitable to be incorporated in a topical preparation.

Stability Study for the Best Formula

Stability study was carried out according to ICH guidelines by keeping selected niosomal dispersion F15 for a period of one month at separate storage conditions. That is, refrigeration temperature 2-8°C and room temperature 25°C. Every week, sample was withdrawn and percent entrapment efficiency, drug release, PH and clarity were determined and results are shown in Table 4. It was observed that slight non-significant reduction in entrapment efficiency and drug release at room temperature and refrigeration temperature, while no changes in pH and clarity observed. This indicated the stability of the prepared niosomal dispersion which reflects the efficiency of the applied method as well as the type and amount of materials used. Similar results observed with niosomal dispersion of clarithromycin.³⁷

CONCLUSION

Thin film hydration technique was used to successfully prepare niflumic acid niosomal dispersion using various cholesterol and surfactant ratios (span 60, span 40, tween 60, tween 80) and dicetyl phosphate (DCP). The best formula had excellent entrapment efficiency, physical appearance, zeta potential, particle size and *in-vitro* release with initial burst effect that persist for 24 hours, therefore, It can be used to create a suitable once-daily topical dosage form that deliver the drug to the

**Figure 5:** Zeta potential of the selected formula (F15).**Table 5: A)** Stability parameters of selected formula F15 at refrigeration temperature.

Parameters	Initial	Week 1	Week 2	Week 3	Week 4
Entrapment efficiency %	91.55%	91.53%	91.45%	90.32%	89.25%
Drug release % after 24 hours	96.98%	96.2%	95.1%	94.6%	94.29%
PH	6.82	6.82	6.80	6.79	6.78
Clarity	Clear	Clear	Clear	Clear	Clear

Table 5: B) Stability parameters of selected formula F15 at room temperature.

Parameters	Initial	Week 1	Week 2	Week 3	Week 4
Entrapment efficiency %	91.55%	90.83%	89.84%	88.63%	88.22%
Drug release % after 24 hours	96.98%	93.42%	92.21%	90.86%	89.52%
PH	6.82	6.82	6.75	6.71	6.68
Clarity	Clear	Clear	Clear	clear	Clear

desired site while reducing side effects and local irritation, resulting in better patient adherence.

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