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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Niosomal Topical Gel Containing Monoammonium Glycyrrhizinate

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ABSTRACT

The aim of present study to formulation and evaluation of niosomal topical gel containing Monoammonium Glycyrrhizinate. However the product has a drawback of poor bioavailability due to high molecular weight, less residence time. These problem can be reduced by the niosomal topical gel formulation. Niosomal formulation were prepared using various surfactants (span20, span40, span60, span80) in the presence of cholesterol in different ratios (1:1, 1:2) by thin film hydration technique. They were evaluated for Appearance, pH, entrapment efficiency and in vitro drug release. Optimized formulation of niosomal suspension F6 using cholesterol and span 60 in the ratio 1:2 shows higher entrapment efficiency of the vesicles and invitro sustained drug release showed high retention of (Q12h= 70.50) the vesicles. The optimized formulation was formulated as topical gel using carbopol and HPMC K4M in different ratios and evaluated for gelling capacity, pH, viscosity, invitro drug release, drug content, isotonicity study, stability study. Optimized formulation of niosomal topical gel (G3) showed higher drug content 93.80% &showed maximum sustained release 70.50 % for a period of 12 hrs. It was concluded that niosomal topical gel is viable alternative for conventional gel and provide localized drug delivery and ability to sustain drug release.

Keywords: *Niosome, Monoammonium Glycyrrhizinate, topical drug delivery.*

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INTRODUCTION

Glycyrrhizaglabra L. is a perennial shrub belonging to the family of Leguminosae. It contains triterpene saponins (3–5%), mainly glycyrrhizic acid (a derivative of glycyrrhetic acid), and flavonoids (1–1.5%). Triterpene saponins have an anti-inflammatory activity due to the strengthening of the glucocorticoid activity [1-5]. Recent studies demonstrate that licorice extracts are useful in the treatment of dermatitis, eczema, and psoriasis, with an efficacy comparable to that of corticosteroids. The characterization of the ammonium salt of glycyrrhizic acid is anti-inflammatory activity. The topical application of this compound as an anti-inflammatory agent can be improved by using various drug delivery systems, e.g., niosomes, which can enhance the permeation through the skin stratum corneum and hence promote the dermal pharmacological action [6-8].

Niosomes are non-ionic surfactant vesicles capable of entrapping hydrophilic and hydrophobic molecules. Niosomes are unilamellar or multilamellar vesicles formed from synthetic, non-ionic surfactant of alkyl or di-alkyl polyglycerol ether class. Niosomes can entrap solutes like liposomes, it is more stable in vitro, and it can improve the stability and duration of action of an entrapped drug as compared to the conventional dosage forms. Niosomes have been several advantages such as higher chemical stability, contact time, and skin penetration enhancing properties. Better targeting of drugs to the infected organ scan be achieved by niosomal formulation due to the presence of non-ionic surfactants with lipids. The presence of non-ionic surfactants increases the permeability of Monoammoniumglycyrrhizinate through the biological membrane and also reduces the systemic toxicity of anti-infective drugs. Drug deposition and entrapment efficiency were the key parameters involved in the formulation of topical Niosomal gel. The number of formulation and processing variables are involved during niosome preparation may affect these parameters and hence the performance of the formulation [9-13].

MATERIAL AND METHODS

Materials:

Monoammonium Glycyrrhizinate is obtained as a gift sample from Sunpure herbal extract pvt.Ltd. Cholesterol was purchased from Research Lab Fine Chem Industries, Mumbai. Surfactant span20 and span 80 was purchased from Lobachem Mumbai, span 40was purchased from, Mylochem Mumbai and span 60 was purchased from Ozone Pharmaceutical, Mumbai. The other chemicals, reagents and solvents used like potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, chloroform, and methanol were of analytical reagent grade.

Preformulation studies:

General procedure for the preparation of calibration curve of UV

Glycyrrhizin10 mg was accurately weighed and dissolved in a sufficient volume of phosphate buffer in a 100 mL volumetric flask. The final volume was made up to the mark with phosphate buffer to obtain a concentration of 100 µg/mL. This stock solution was used to prepare further standard solution of the drug. From the stock solution, aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 mL of volume, up to 10 ml were transferred to a series of 10 mL volumetric flask and the volume was made up to the mark with phosphate buffer pH 7.4. Thus, drug solution concentration obtained was in the range of 5-50 µg/mL. All the solution was filtered using Whatman filter paper (# 41). The absorbance of all the resultant solutions was measured against blank using a UV Double-beam spectrophotometer (Shimadzu 1700, Japan) at 251 nm [14].

Drug-Excipient Compatability Study:

The compatibility between the drug, chosen cholesterol and nonionic surfactants, and other excipients has been checked by using FTIR peak matching method. FTIR study has no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals. The drug excipient compatability studies was studied by comparing the interpretation data of FTIR of pure drug with the FTIR of various excipients like cholesterol, non-ionic surfactants & finally with niosomal formulation [15].

Procedure for the Preparation of Monoammonium Glycyrrizinate Niosomes:

The eight formulayion of niosomes were prepared by using thin film hydration technique using rotary evaporator. The mixture of vesicles forming ingredients like surfactant and cholesterol were dissolved in a volatile organic solvents chloroform and ethanol (1:2) in a round bottom flask. The organic solvent was then removed above the lipid transition temperature by using rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film could be rehydrated with 10 mL of aqueous phase (pH 7.4 buffer) at 0-60 °C with gentle agitation. This process formed typical multilamellar niosomes [16].

Table 1: Formulation of Niosomes

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	50	50	50	50	50	50	50	50
Cholesterol(mg)	100	100	100	100	100	100	100	100
Span 20(mg)	100	200	-	-	-	-	-	-
Span 40(mg)	-	-	100	200	-	-	-	-
Span 60(mg)	-	-	-	-	100	200	-	-
Span 80(mg)	-	-	-	-	-	-	100	200
Chloroform: Ethanol ratio	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2
PBs(pH 7.4) (ml)	10	10	10	10	10	10	10	10

Characterization of Niosomes

Drug Content:

The amount of drug in the formulation was determined after lysing the niosomes using 50% n-propanol and shaken well for the complete lysis of vesicles. After suitable dilution with the phosphate buffer saline pH 7.4 the absorbance of the solution was measured at 254 nm in the UV visible spectroscopy using empty niosomes as blank. The drug content was calculated from standard curve using formula [17].

$$\text{Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

Entrapment Efficiency(EE):

Niosomes entrapment efficiency was estimated by Ultracentrifugation method where the dispersion of niosomes were centrifuged at 14000 rpm for 90 minutes. The clear supernant from the resulting centrifuged solution was diluted using pH 7.4 phosphate buffer and analyzed for Monoammonium

Glycyrrhizinate ate spectrophotometrically and the percentage entrapment efficiency (EE %) was calculated using the following equation [18]:

$$\text{Entrapment Efficiency} = \frac{\text{SampTotal drug – Diffused drugle absorbance}}{\text{StandaTotal drugrd absorbance}} \times 100$$

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

In-vitro drug release study of niosomal formulation was studied by membrane diffusion technique. In vitro diffusion cell was made using cellophane membrane which was previously soaked in warm water for activation. The diffusion cell consists of a beaker, magnetic stirrer with temperature control and test tube with both ends open. One end of the test tube was closed using treated cellophane membrane and the other end was kept open to introduce niosomal formulation. The diffusion medium was freshly prepared buffer saline (pH 7.4) of 100 ml and maintained temperature 37ºC ± 0.5ºC. The niosomal formulation 5 ml was placed inside the diffusion cell through open end of the test tube on the cellophane membrane. Aliquots (5ml) of medium were withdrawn periodically and replaced with fresh diffusion medium of phosphate buffer (pH 7.4) to maintain constant volume (sink condition). The samples were analyzed for drug using a UV-Vis spectrophotometer at 251 nm [19].

Stability study:

The optimized Monoammonium Glycyrrhizinate niosome formulation (F6) was examined for stability study. The formulations were taken in a 20 ml sealed glass vial and stored in three different environments such as 4°±20C, room temperature and 40°C±20C,75% ±5%RH for a period of three months. Samples from each batch were withdrawn at the interval of one month and evaluated for entrapment efficiency and in vitro drug release [20].

Procedure for formulation of niosomal topical gel

Niosomal base gel of Monoammonium Glycyrrhizinate was prepared by dispersing the weight amount of the Carbopol-934 and HPMC k15 in a sufficient quantity of distilled water. After complete dispersion, the solution was kept in dark for 24 hrs for complete swelling of carbopol-934. The Carbopol and HPMC dispersion was mixed with selected formulations containing Monoammonium Glycyrrhizinate in excipients. The mixture was stirred well to get homogenous solution so that concentration of carbopol 934 will become 0.5% w/w. the appropriate amount of triethanolamine was added to maintain the pH with continuous stirring to get homogenous gel [20, 21].

Table 2: Formulation of Niosomal gel

Sr.no.	Ingredients	G1	G2	G3	G4
1	Niosomal dispersion (ml)	10	10	10	10
2	Carbopol %w/v	1	1	1	1
3	HPMC K4M %w/v	0.5	1	1.5	2
4	Methyl paraben	0.1	0.1	0.1	0.1
5	Glycerine	5	5	5	5
6	Triethanolamine	Q.S.	Q.S.	Q.S.	Q.S.

Characterization of niosomal gel:[22-27]

Appearance:

The formulations were observed for the presence of any particular matter. Clarity is one of the most important features of topical preparations. The appearance and clarity is determined by visual testing.

pH:

Ophthalmic formulations should have a pH ranging between 5.5 and 6.5. The developed formulations were evaluated for pH by using a digital pH meter.

Drug content:

1.0 gm of each gel formulation were taken in 100 ml of volumetric flask containing 20 ml of phosphate buffer saline (pH 7.4) and stirred for 30 minute. The volume was made upto 100 ml & 1ml of the above solution was further diluted to 50 ml with phosphate buffer saline (pH 7.4). The resultant solution was filtered through membrane filter. The absorbance was recorded by using UV spectrophotometer at respective absorption maxima of monoammonium glycyrrhizinate 251 nm respectively. Drug content was determined from the calibration curve.

Viscosity Studies:

Viscosity of the formulations was determined using Brookfield viscometer (AmetekDV2T) fitted with S-6 spindle at 10, 20, 50 and 100 rpm.

Spreadability:

It is determined by apparatus which consists of a wooden block, which is provided by a pulley at one end. The spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of niosomal gel. A ground glass slide is fixed on this block. An excess of niosomal gel (about 2 g) under study is placed on this

ground slide. The niosomal gel is then sandwiched between this slide and another glass slide. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the niosomal gel between the slides. By putting weight of 1kg, the time (in seconds) required by the top slide to cover a distance of 7.5 cm with the help of string attached to the hook is noted.
A shorter interval indicates better spreadability, which is calculated by the formula:

$$S = \frac{M \times L}{T}$$

Where,
S=Spreadability,
M=Weight tied to upper slide,
L=Length of glass slides
T=Time taken to separate the slides completely from each other.

***In-vitro* of drug release:**
The diffusion cell consisted of a hollow glass cylinder .one end of the cylinder was covered with dialysis membrane which was previously soaked in warm water for 24 hrs. The diffusion cell was placed in a 500ml beaker that served as the receptor cell and the temperature was maintained at 37^0C. Buffer saline (100 ml) pH 7.4 was placed in the receptor cell. Sample withdrawn at specified time intervals and the medium volume was make up with fresh buffer saline (pH7.4).

Stability study:
The present study involves investigation of the stability of the formulated niosomal gels under influence of 40°C ± 2°C, 75% RH ± 5%, storage conditions for a period of 3 months. The study was carried out to evaluate the effect of storage conditions on essential attributes of gels such as appearance, pH, Viscosity, drug content & in-vitro diffusion studies after specified time intervals.

RESULTS AND DISCUSSIONS

Characterization of niosome

Standard Calibration Curve of Monoammonium glycyrrhizinate in UV Spectrophotometer

Standard Calibration Curve of Monoammonium Glyyrrhizinate in UV Spectrophotometer
The UV absorbance's of Monoammonium Glyyrrhizinate standard solutions in the range of 2-12 µg/ml of drug in buffer pH 7.4 showed linearity at λmax 251 nm. The linearity graph plotted for absorbance (A) against concentration (C) with R^2 value 0.996 and with the slope equation y=0.058 × -0.012. The absorbance values and standard curve were in figure 2.

Table 3: Standard calibration curve of drug by UV spectrophotometer in PBS 7.4

Sr.No.	Conc.ug/ml	Absorbance
1	10	0.065
2	20	0.133
3	30	0.195
4	40	0.247
5	50	0.30

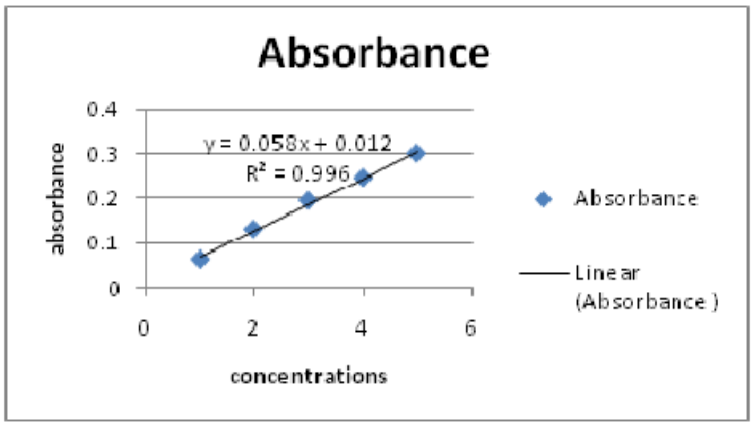

Figure 2: Standard calibration curve of Monoammonium glycyrrhizinate drug

Drug-Excipient Compatibility Studies

By analyzing the FTIR study of pure drug and formulation it has been concluded that there is no interaction between drug and excipients.

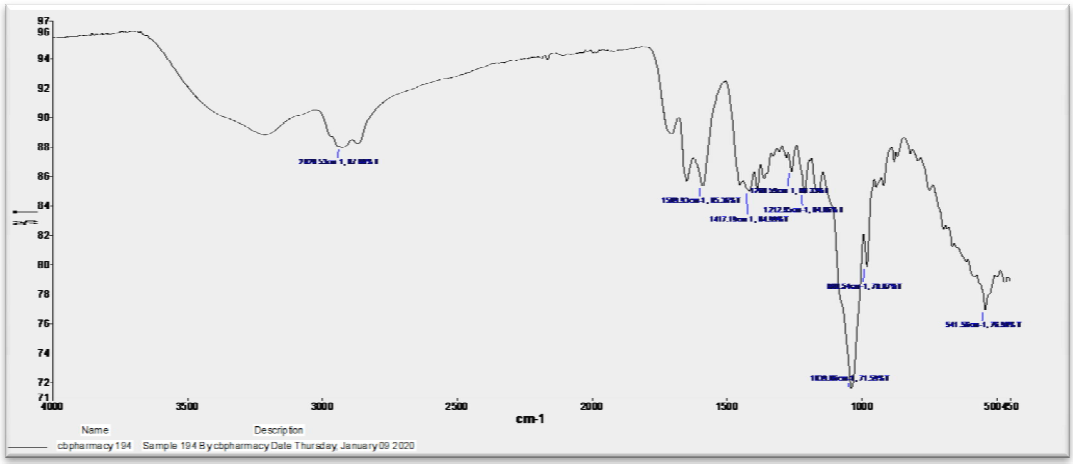

Figure 3(a) FTIR of Monoammonium Glycyrrhizinate drug

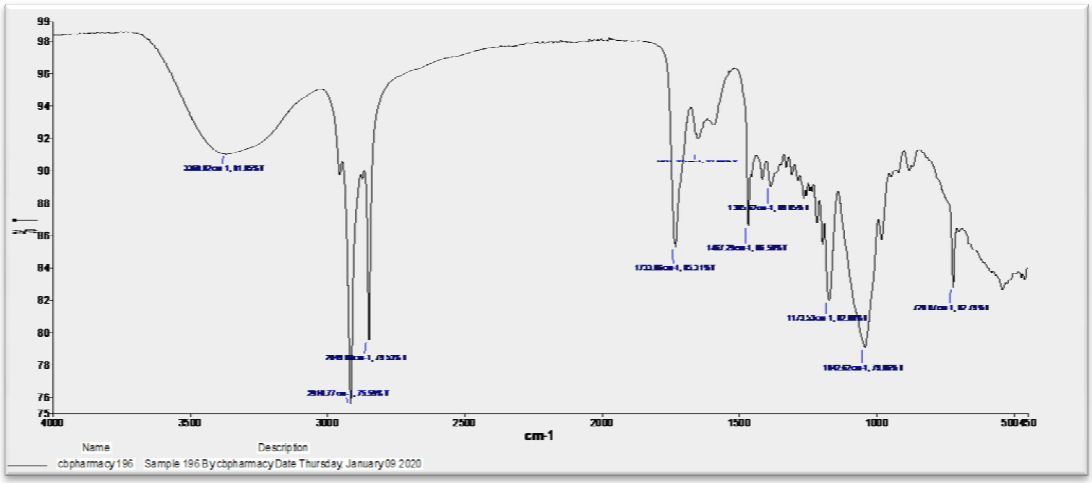

Figure 3(b): FTIR of Monoammonium Glycyrrhizinate noisome

Table 4: Interpretations of FTIR spectra of niosomal formulation

S N	Types of observation	Reported frequency cm-1	Observed frequency cm-1
1	C-O stretching	1260-1000	1039.06
2	C-H stretching	2950-2850	2929.53
3	O-H stretching	3550-3200	3260.64
4	N-H bending	3300-3500	3420.12

Drug Content and pH

The drug content study of all eight batches have been calculated by the lysis of niosomes in 5% n-prpanol and assay was made by UV spectrophotometer. From all these batches F6 batch showed highest drug content (93.23%) of drug. In all six batches F6 batch gives optimum pH.

Table 5: Drug content and pH

Formulation code	pH	Drug content (%)
F1	5.1	89.59±1.28
F2	4.9	90.60±1..23
F3	4.9	91.13±1.19
F4	4.7	92.16±0.67
F5	4.7	87.23±1.87
F6	**4.7**	**93.23±1.01**
F7	5.1	81.23±0.74
F8	5.2	80.41±0.56

Drug Entrapment Efficiency

The entrapment efficiency of all eight batches has been determined by centrifugation method. From all these batches F6 batch that showed highest entrapment (83.91 %) of drug. Hence, F6 batch was considered as an optimized batch as given in below table 5.

Table 6: Percentage of drug entrapment efficiency of niosomal formulation

Sr.No.	Formulation code	Entrapment efficiency
1	F1	30.34
2	F2	28.40
3	F3	60..47
4	F4	58.82
5	F5	71.48
6	**F6**	**83.91**
7	F7	62.88
8	F8	60.57

***In Vitro* Drug Release Study**

The in-vitro release of Monoammonium Glycyrrhizinte niosomal formulations checked using the dialysis membrane and measured the release at 1 hr, 2 hr and 3 hrupto12 hrs. After, examining percentage cumulative drug release graph of all formulation, the F6 batch showsslower and prolonged drug release than the other formulations (70.50 %) at 12hrs. Hence, the F6 batch was concluded as an optimized batch.

Table7 Invitro drug release of Monoammonium Glycyrrhizinate niosome

Time (hr)	%Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	9.12	10.20	11.69	11.45	6	4	13.39	10.
2	15.20	16.15	17.28	20.57	12.7	7.12	17.89	15.5
3	18.22	22.25	23.67	26.45	15.34	14.76	24.56	18.34
4	20.12	28.13	29.55	33.16	20.34	19.98	30.12	21.54
5	24.35	32.16	33.44	39.12	25.12	23.12	34.54	26.12
6	30.50	39.60	40.45	43.56	29.23	26.11	40.12	35.23
7	39.12	47.70	49.66	50.60	34.60	33.76	44.56	46.12
8	51.34	53.55	54.60	56.46	40.35	43.87	53.43	53.43
9	59.23	64.62	59.34	61.60	46.68	47.99	59.23	61.23
10	65.12	71.94	65.76	67.50	54.98	51.56	61.23	68.64
11	73.20	78.68	70.12	72.60	60.56	59..29	67.34	75.12
12	79.60	83.25	75.20	76.12	75.70	70.50	73.20	79.50

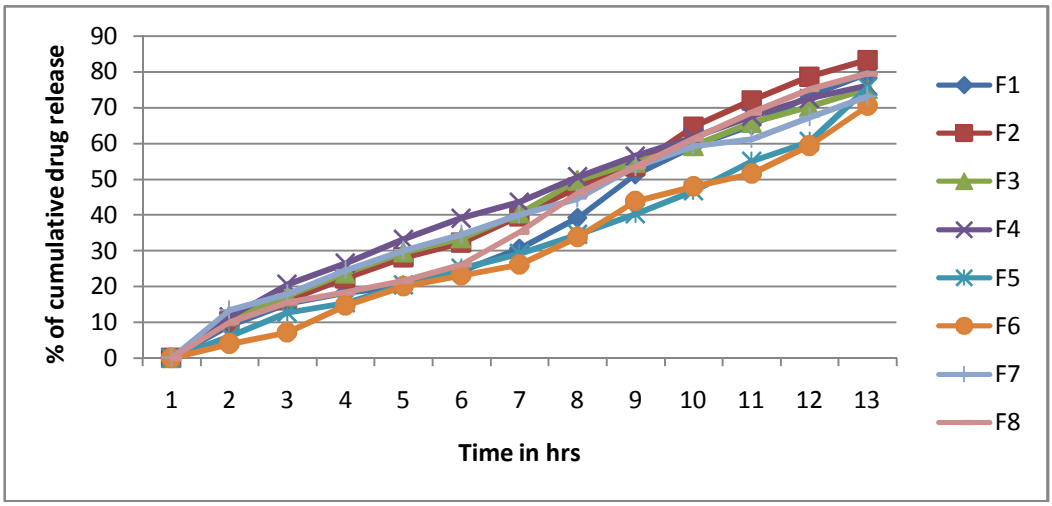

Figure 4 Cumulative % drug releases of Monoammonium Glycyrrhizinate niosome

Stability Studies

Stability studies on optimized F6 batch of Monoammonium glycyrrhizinate niosome preparation have been conducted for 90 days in different temperature conditions and have evaluated for physical

appearance, pH, drug entrapment efficiency, drug content and in-vitro drug release as a function of the storage condition. The niosomes stored at 4ºC were found to be stable for the duration of 90 days as compared to room temperature and accelerated stability temperature. The results were showed in table 8.

Table 8: Stability studies of optimized batch

Temperature	Percentage entrapment after one month (%)	Percentage entrapment after two month (%)	Percentage entrapment after one three (%)
4⁰C	83.91	83.85	83.80
Room temperature	83.74	80.90	79.89
40⁰C±2⁰C, 75±5%RH	80.75	78.85	75.90

Table 9: *In vitro* release study of optimized formulation at initial and after stability study

Time in hr	% Cumulative drug release after stability			
	Initial	At 4⁰C	At Room Temp.	At 40 ⁰C
1	4	3.99	3.74	1.99
2	7.12	6.17	6.00	3.50
3	14.76	17.24	17.09	14.11
4	19.98	20.22	20.17	16.50
5	23.12	23.50	22.75	18.45
6	26.11	28.10	26.82	24.57
7	33.76	32.45	30.44	27.25
8	43.87	44.20	42.50	40.23
9	47.99	48.15	47.25	44.12
10	51.56	50.50	48.55	45.26
11	59..29	53.20	52.10	49.54
12	70.50	70.08	69.66	53.24

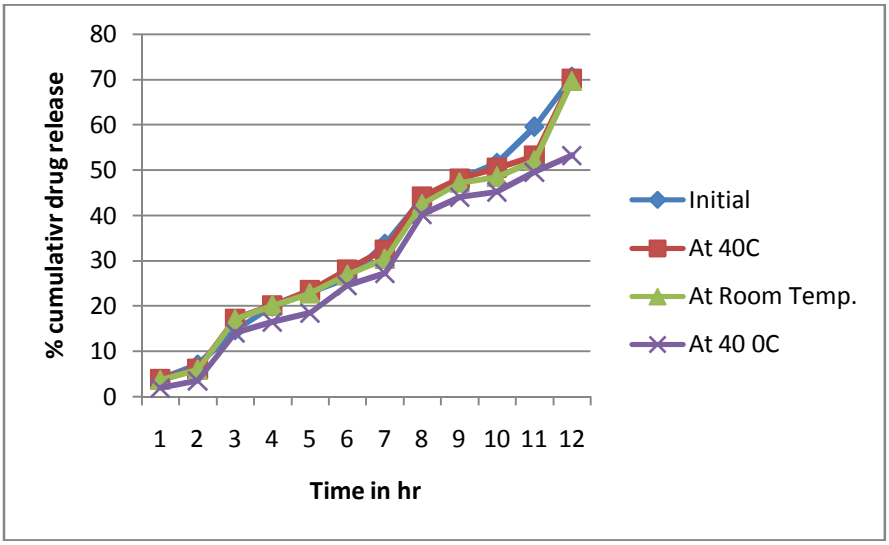

Figure 5: In vitro drug releases at initial and after stability

Characterization of Niosomal Topical Gel

Appearance:

The appearance of niosomal gel was translucent and off- White in colour.

Drug content and pH

The drug content study of all four batches have been calculated by the dilution of niosomal gel in 100ml phpsphate buffer pH 7.4 and assay was made by UV spectrophotometer. From all these batches G3 batch showed highest drug content (97.80%) of drug. In all six batches G3 batch gives optimum pH.

Viscosity and spreadability:

The niosomal gel shows viscosity from 42000-68500cps. Viscosity of niosomal gel depends on the concentration of gelling agent.

The G3 formulation shows highest spreadability, shorter interval showed the better spreadability.

Table 10: pH, Drug content, viscosity and spreadability

Formulation code	pH	Drug content	Viscosity (cps)	Spreadability (gms.cm/sec)
G1	6.4	94.50	42700	54.5
G2	6.4	95.86	46800	42.85
G3	6.5	97.80	52400	66.6
G4	6.3	96.25	68400	60.0

***In-vitro* drug release:**

The prepared gel formulations released 65.40% (G1), 63.15 % (G2), and 71.55 %(G3), and 66.29 %(G4) of drug after 12 hrs. In G3 formulation concentration of Carbopol 934 and HPMC K4M have shown good *in-vitro* drug release.

Table 11: *In vitro* drug release of Monoammonium Glycyrrhizinate niosomal gel

Time in hrs	G1	G2	G3	G4
1	9.8	7.5	9.0	8.5
2	14.42	13.60	16.50	16.50
3	19.42	20.40	21.13	21.56
4	24.78	23.78	27.60	33.70
5	27.15	27.17	31.44	36.12
6	33.86	31.80	34.49	42.11
7	39.80	37.26	41.26	45.26
8	43.60	43.33	49.12	49.80
9	47.30	46.20	55.50	53.12
10	54.22	51.80	60.60	56.24
11	60.33	54.52	66.33	62.33
12	65.40	63.15	71.55	66.29

Stability study:

Stability studies on optimized G3 batch of Monoammoniumglycyrrhizinate niosomal gel preparation have been conducted for 3 months in 40^0C± 2°C, 75% RH ± 5% and have evaluated for physical appearance, pH, drug entrapment efficiency, drug content and in-vitro drug release as a function of the storage condition, there is no significant change occur in formulation.

Table 12: Stability studies of optimized batch

Sr.No.	Parameters	After 1 month	After2 month	After3 month
1	Appearance	Nc	Nc	Nc
2	viscosity	Nc	Nc	Nc
3	pH	6.5	6.5	6.5
4	Drug content	97.80	97.20	96.10

CONCLUSION:

It is concluded that the thin film hydration technique is a useful method for the successful incorporation of drug Monoammonium Glycyrrhizinate into niosomes with high entrapment efficiency. From the study it can be concluded that the niosomal topical gel is a viable alternative to conventional topical gels as it enhances bioavailability by prolonging the contact time of the drug with the corneum striatum and its ability to release the drug in a sustained manner. It also results in better patient compliance by reducing the frequency of administration. Hence we can conclude the niosomal topical gel formulations used as drug carriers to enhance the bioavailability of topical drug delivery.

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