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DEVELOPMENT AND EVALUATION OF HYDROCORTISONE-LOADED NIOSOMAL GEL

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Keywords:

Niosomal gel, Hydrocortisone, Thin-film hydration method, Topical drug delivery, Novel formulations

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ABSTRACT: Objective: The present research work was to formulate optimize and evaluate hydrocortisone-loaded niosomal gel for the management of rheumatoid arthritis. **Method:** Niosomal gel was successfully prepared by lipid-thin film hydration process and optimized by using 2^3 full factorial designs using three independent variables (tween 80 concentration, cholesterol concentration, and sonication time) and three dependent variables (cumulative drug release, mean particle size and entrapment efficiency). The effect of all variables was assessed by response surface methodology. **Results:** The prepared formulations were evaluated in terms of particle size, *in-vitro* drug release, encapsulation efficiency, zeta potential, viscosity, and spreadability. Based on response surface methodology, S6 formulation was found to be the best formulation with entrapment efficiency of 92.27%, *in-vitro* drug release of 75.61% in 8 hrs, and mean particle diameter of 121.58 nm. The stability studies indicated that all the formulations are stable as none exhibited significant drug content change over time. **Conclusion:** The study indicated the successful development of hydrocortisone-loaded niosomal gels with improved penetration, good homogeneity, and enhancement of duration of action. It can thus be concluded that the developed gel could be an effective treatment for rheumatoid arthritis.

INTRODUCTION: Hydrocortisone acetate belongs to the class of corticosteroids, which is a synthetic or semi-synthetic derivative of the natural hormone cortisol secreted by adrenal cortex [1, 2]. FDA approved it in 1952 for clinical use in managing inflammatory diseases like rheumatoid arthritis, psoriasis, asthma, eczema, and many more [3, 4]. The conventional therapy with hydrocortiosone is based on systemic delivery by different routes, which leads to serious complications [5-7]. Systematic treatment with conventional formulations may increase health and economic burden by decreasing the therapeutic effects and adverse effect ratio. Hence, adopting an alternative route of administration could be an excellent approach to increase the efficiency of the drug.

The topical route of administration is the most non-invasive route of drug administration as it delivers the drug into the body through the skin and offers the advantage of high drug retention, increasing patient compliance by reducing the frequency of dose with high efficacy and safety [8, 9]. The present work was based on the formulation development, optimization, and evaluation of hydrocortisone-loaded niosomal nanogel for topical delivery. Niosomes are a non-ionic vesicular delivery system that can entrap both hydrophilic and lipophilic

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drugs. These are also called modified liposomes [10, 12]. Niosomal drug delivery system works as drug depots within the body that releases the drug in a controlled manner through its bilayer, providing the enclosed drug to be released with sustained action [13, 14].

MATERIALS & METHODS:

Materials: The chemicals and the drug used in the present study, namely hydrocortisone, cholesterol, and span 40 were purchased from Yarrow Chem Products, Mumbai. Tween 80, Carbopol, and Glycerol were purchased from Nice Laboratory Reagents, Kochi. All reagents were of the highest analytical grade.

Preformulation Study: Active pharmaceutical ingredient (API) was identified by analysis of absorption maxima by UV spectrophotometer in 0.1N hydrochloric acid and phosphate buffer of pH 7.4 using Shimadzu-1700 UV-Visible Spectro-photometer [15, 16] and FT-IR analysis [17, 18].

The melting point study was determined using melting point apparatus. The solubility and partition coefficient of the drug was determined by shake flask method [19]. The solubility was determined in four different solvents: distilled water, ethanol, 0.1 N HCl and phosphate buffer of pH 7.4.

The compatibility of the drug with excipients was assessed by FTIR analysis. The drug was thoroughly mixed with excipients in a ratio of 1:1, and all the samples were stored at 40°C and 75% RH in closed vials for 21 days and then scanned by FTIR. The spectra of pure drugs and mixtures of drugs with excipients were compared with standards to check for any physical and chemical incompatibility [20, 21].

Methods of Preparation of Niosomes: A lipid-thin film hydration method was used to prepare niosomes. Briefly, in a round bottom flask required amount of hydrocortisone was dissolved in 5 ml of ethanol. In a separate beaker, span 40, tween 80, and cholesterol were dissolved in 5 ml of chloroform [22].

Both organic solutions were mixed, and the organic solvent was evaporated until a complete dry film was obtained under reduced pressure using a rotary evaporator [23]. Then this dry film was hydrated using a phosphate buffer of pH 7.4. The compositions of all eight formulations are mentioned in **Table 1.**

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS OF NIOSOMES

Ingredients (mg/10ml)	Formulation Code							
	S1	S2	S3	S4	S5	S6	S7	S8
Hydrocortisone	200	200	200	200	200	200	200	200
Span 40	10	20	10	20	10	20	10	20
Tween 80	150	150	150	150	200	200	200	200
Cholesterol	30	30	50	50	30	30	50	50

Optimization of Various Parameters of Niosomal Gels by Full Factorial Design: The effect of different independent variables on formulation parameters was evaluated using response surface methodology. Full factorial 2^3 Box-Behnken Design led to the development of the eight formulations of hydrocortisone-loaded niosomal gels. The response was calculated by the design of experiment software [24]. Three independent variables were selected, which included Tween 80 concentration (X_1), Cholesterol concentration (X_2) and Sonication time (X_3) as given in **Table 2**, concerning these, three dependent variables were selected, including percent cumulative drug release after eight hours (Y_1) and entrapment efficiency (Y_2) and mean particle diameter (Y3). The three independent variables were selected at two levels, *i.e.*, upper and middle (1, -1) [25].

TABLE 2: THE INDEPENDENT VARIABLES

Factor	Name	Units	Low Level (-)	High Level (+)
A (X_1)	Tween 80	% w/v	150	200
B (X_2)	Cholesterol conc.	% w/v	30	50
C (X_3)	Sonication Time	Sec	10	30

The effect of independent variables on dependent variables at three levels was calculated by using the below mentioned non-linear quadratic model expression, where Y is the dependent variable, b_0 is the arithmetic mean of the nine formulations and b_1- b_{123} were the regression coefficient of respectable variables. The factor X_1, X_2, X_3 indicates the interaction among the various parameters.

$$y_1=b_0+b_1X_1+ b_2X_2+ b_3X_3+ b_{12}X_1X_2+ b_{13}X_1X_3+ b_{23}X_2X_3+ b_{123} X_1 X_2 X_3$$

Characterization of Niosomes:

Particle size Analysis by Beckman Coulter: The particle size of the niosomes was evaluated by Beckman Coulter method [26, 27].

Surface and Shape Analysis by TEM: The shape and surface characteristics of niosomes were analyzed by Transmission Electron Microscope (Model H-7500 Hitachi, Japan) [28].

Zeta Potential Analysis: Surface charge of niosomes was determined by laser Doppler electrophoresis [29, 30].

Drug Entrapment Efficiency (%): The amount of drug entrapped in the niosomes was determined by gel filtration technique. Sephadex G-50 was used for gel filtration to remove the free drug in niosomal dispersion. The entrapment efficiency was determined by lysing the vesicles with Triton X-100 (0.5% v/v) and assayed for drug content using UV Visible spectrophotometer at a wavelength of 241.4 nm. [31, 32]

The percentage drug entrapment efficiency was calculated by using the following equation.

Entrapment efficiency = Observed content / Initial drug content × 100

***In-vitro* Drug Release Studies:** The *in-vitro* drug release studies were performed by Franz diffusion cell using egg membrane. The whole assembly was put on a magnetic stirrer to maintain the required temperature condition and stirred at a speed of 100 rpm [33]. The receptor compartment of diffusion cell was filled with the required amount of phosphate buffer (pH 7.4). Niosomes equivalent to 200 mg of drug was placed on the egg membrane. At appropriate time interval 1 ml aliquot of the receptor medium was removed and instantly replaced by an equal volume of fresh phosphate buffer (pH 7.4) to maintain the sink conditions [34, 35]. The sample was analyzed spectrophotometrically at λ_{max} 241.4 nm for *in-vitro* drug release studies.

Stability Studies: Stability studies were performed on optimized formulation S_6. The formulation was stored in air tight container at 25±2 °C/60±5% relative humidity (RH), 40±2 °C/75±5% (RH) for 90 days. Samples were examined for residual drug content after a period of 15, 30, 45, 60 and 90 days [36, 37]. Initial drug content was taken as 100% for each formulation.

Characterisation of Gels: The formulated niosomal dispersion was converted in to nanogel by adding 1% carbopol with continuous stirring at 1200 rpm and characterized by using different parameters.

Physical Appearance: The prepared niosomal gel was examined visually for its color, clarity, homogeneity and appearance [38].

pH Stability Study: 2.5 g of gel was accurately weighed and dispersed in 25 ml of distilled water. The pH of the dispersion was measured by using a digital pH meter [39].

Spreadability: The spreadability of gel formulations was determined by using spreadability apparatus. 1.0 g of gel sample was kept on the lower slide, and the upper slide was placed on top of the sample. The spreadability was determined by using the following [40].

$$S = m \times l\, t$$

Viscosity: The viscosity of the niosomal gel was determined at 22^{o}C by Brookfield Viscometer [41].

Gel Strength: The apparatus for measuring gel strength consists of a plunger with a pan to hold weights at one end, whereas the other is immersed into the gel.

The gels were placed in a glass bottle where marking was done 1cm below the filling mark. The weight required for the plunger to sink to a depth of 1 cm through the prepare gel was measured for each formulation [42, 43].

RESULTS AND DISCUSSION:

Preformulation Studies:

Preformulation Studies of Drug: The drug was identified by different methods, including melting point method, UV spectroscopy and FTIR spectroscopy. All the parameters were found within limits and complied with the requirements of the official compendia. UV spectra of the drug showed maximum absorbance at the wavelength 241.4 nm. The melting point of the drug was found in a range of 218-220°C (reported value- 219-223°C), confirming the purity of the drug.

Partition Coefficient: The drug's partition coefficient was found to be 1.63, which is in the acceptable range when compared with standard drug.

Solubility of Drug: The drug was found to be remarkably soluble in phosphate buffer, propylene glycol, and ethanol and slightly soluble in purified water.

Drug Excipient Compatibility Study: The result of physical and chemical incompatibility analysis indicates that the API is compatible with all the excipients used in the formulations.

Optimization of Various Parameters by Full Factorial Design: The results obtained after implementing 2^3 Full Factorial designs are mentioned below.

For Y_1: Cumulative Drug Release (%): The regression equation for cumulative drug release obtained after calculation of main and interaction effects is represented in the given equation. The corresponding Pareto chart is shown in **Fig. 1.**

$$y_1=62.56+3.84X_1-3.06X_2+2.20X_3-1.47X_1X_2-0.083X_1X_3-1.11X_2X_3-1.42X_1X_2X_3$$

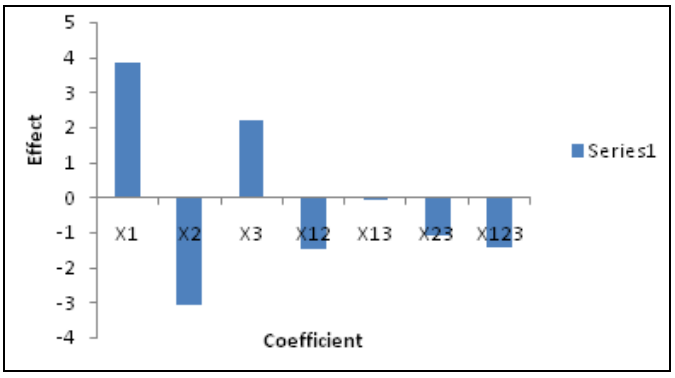

FIG. 1: PARETO CHART (Y_1)

As per polynomial equation, factor X_1 (concentration of tween 80) directly effects the drug release from niosomes, X_2 (concentration of cholesterol) inversely affects the drug release from niosomes, and X_3 (sonication time) positively increases drug release. The simultaneous effects of all the variables are negligible.

For Y_2: Entrapment Efficiency (% w/w): The regression equation for entrapment efficiency obtained after calculation of main and interaction effects is represented in the given equation, and the corresponding Pareto chart is shown in **Fig. 2.**

$$Y_2=82.21-3.36X_1+2.01X_2-1.93X_3-2.33X_1X_2+1.98X_1X_3-1.11X_2X_3-4.00X_1X_2X_3$$

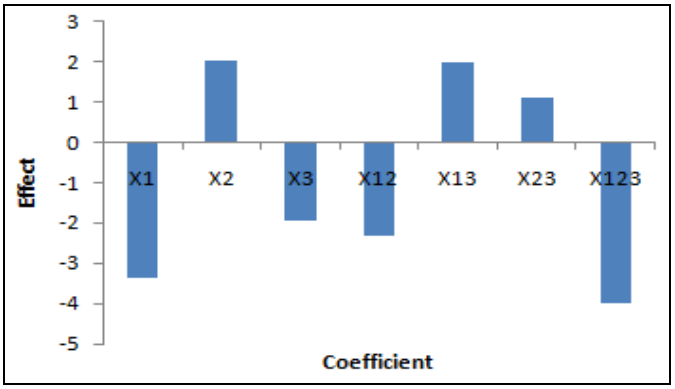

FIG. 2: PARETO CHART (Y_2)

As per polynomial equation, as the concentration of tween 80 (X_1) increases, the entrapment efficiency decreases, as concentration of cholesterol (X_2) increases, the entrapment efficiency increases, sonication time (X_3) also had a negative effect entrapment efficiency.

For Y_3: Mean Diameter (µm): The regression equation for mean diameter obtained after calculation of main and interaction effect is represented in the given equation, and the corresponding Pareto chart is shown in **Fig. 3.**

$$Y_3=116.18-2.28X_1+4.47X_2-5.185X_3+1.8X_1X_2-0.37X_1X_3+0.62X_2X_3-1.11X_1X_2X_3$$

As per polynomial equation, both concentration of tween 80 (X_1) and sonication time (X_3) negatively affect the particle size.

On the other hand, as the concentration of cholesterol (X_2) increases, the particle size increases. The simultaneous effects of all the variables are negligible.

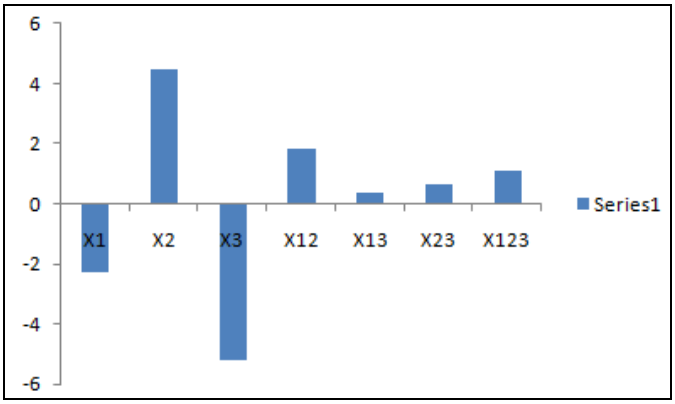

FIG. 3: PARETO CHART (Y_3)

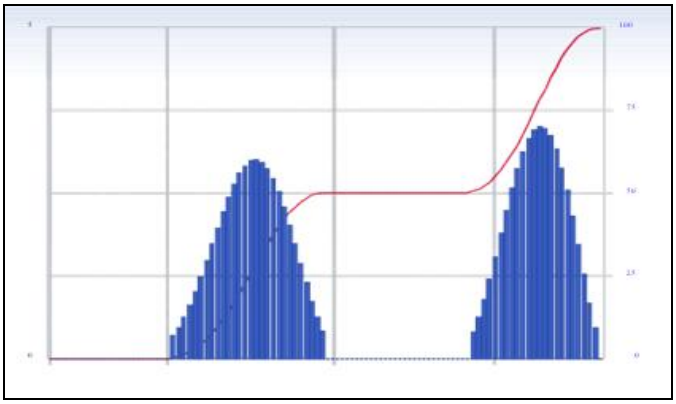

FIG. 4: PARTICLE SIZE DISTRIBUTION

Characterization of Niosomes:

Particle size Analysis by Beckman Coulter: The particle size analysis was performed by beckman coulter, and the average size of particles was found to be 121.58 nm as shown in **Fig. 4.**

Surface Analysis and Shape by TEM: The surface morphology of the niosomes was examined by TEM. Niosomes were spherical, smooth, vesicular in nature, and morphologically similar without agglomerations, as shown in **Fig. 5**.

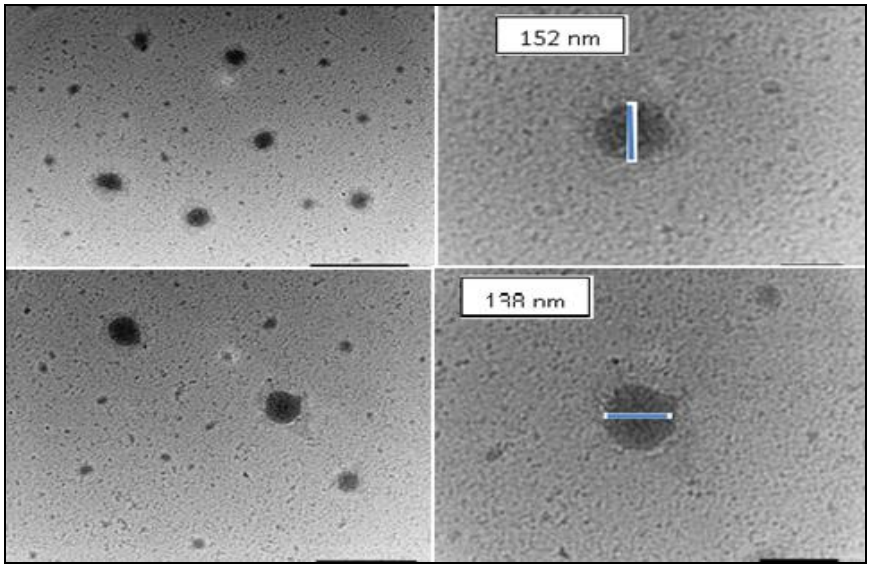

FIG. 5: TEM IMAGE OF HYDROCORTISONE-LOADED NIOSOMAL DISPERSIONS (F6)

Zeta Potential Analysis: Zeta potential analysis was done by Beckman Coulter, zetasizer and average Zeta potential was reported to be -0.68 (mV), as shown in **Fig. 6.**

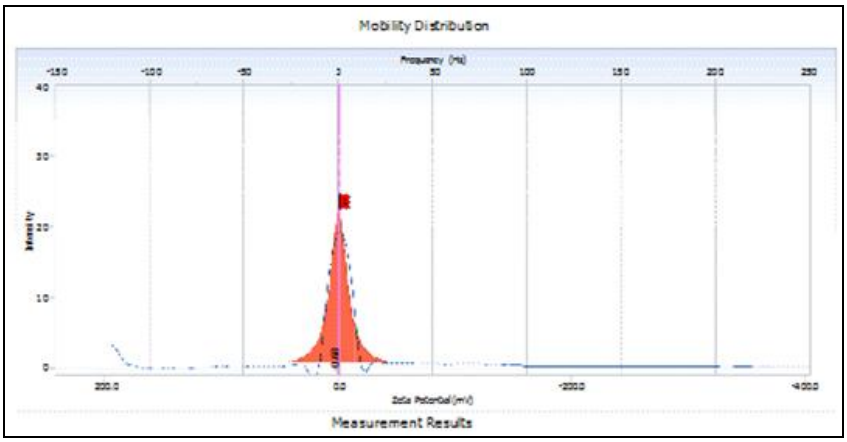

FIG. 6: ZETA POTENTIAL ANALYSIS

Entrapment Efficiency: The entrapment efficiency of eight formulations (S1-S8) is summarized in **Table 3.**

TABLE 3: ENTRAPMENT EFFICIENCY OF NIOSOMES

Batch Code	Entrapment Efficiency (%) ± S.D.
S1	67.28 ± 0.59
S2	69.09± 1.12
S3	71.10± 0.89
S4	74.13 ± 1.19
S5	87.36± 1.34
S6	92.27± 0.17
S7	84.74 ± 1.15
S8	80.78 ± 1.90

***In-vitro* Drug Release Study:** The drug dissolution study of eight formulations (S1-S8) is depicted in **Fig. 7.**

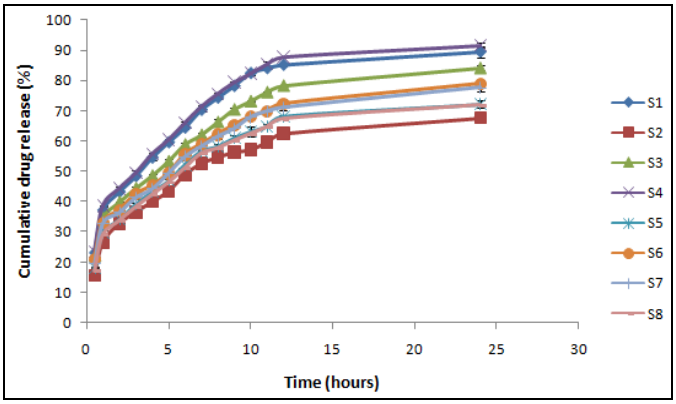

FIG. 7: *IN-VITRO* DRUG RELEASE PROFILES OF NIOSOMES

Stability Studies: The stability studies at 25±2 °C/60±5% RH (room temperature) indicated good stability of all formulations as there was no significant change in the drug content. However, the drug degradation was fast at 40±2 °C/75±5% (RH). Thus the ideal temperature is at room temperature.

Characterization of Drug-Loaded Niosomal Gel:
Appearance: The developed niosomal gel was found to be white translucent with uniform and soft texture.

pH Measurement: The pH of hydrocortisone-loaded niosomal gel was found to be within acceptable limits, thus indicating suitability for skin application.

Spreadability Study of Gel: The spreadability of drug-loaded niosomal gel was found to be 18.75 gm cm/sec±0.1, which is in an acceptable range.

Viscosity: The viscosity of the placebo carbopol gel, pure drug-loaded gel and drug-loaded niosomal gel was determined at room temperature. The placebo carbopol 934 gel exhibited more viscosity than hydrocortisone-loaded niosomal gel. The viscosity of placebo carbopol gel, pure drug-loaded gel, and hydrocortisone-loaded niosomal gel were found to be 22.01 Pa's, 22.10 Pa's and 6.95 Pa's, respectively. The viscosity of the niosomal gel was found to be in acceptable limits.

CONCLUSION: The study indicated the successful development of hydrocortisone-loaded niosomal gels with improved penetration, good homogeneity, and enhancement of duration of action. The developed nano gel formulations were evaluated in terms of particle size, entrapment efficiency, *in-vitro* drug release, zeta potential, viscosity, spreadability and stability studies. Based on the response surface methodology results, the S6 formulation is considered the best formulation with the highest entrapment efficiency and *in-vitro* drug release rate. The results of stability studies indicate that the formulation was stable at room temperature with negligible drug loss. It can thus be concluded that the developed gel could be an effective treatment for rheumatoid arthritis.

CONFLICTS OF INTEREST: None

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