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# Formulation, Development and Evaluation of Nanoemulgel of Cyproheptadine Hydrochloride

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**ABSTRACT:**
The objective of present research work was to formulate Nanoemulgel of Cyproheptadine HCl for the treatment of allergic reaction. By using $3^2$ full Factorial Design optimization of Cyproheptadine HCl Nanoemulsion was done & optimized Nanoemulsion was incorporated into gel & Nanoemulgel of Cyproheptadine HCl was formulated. Spectrometric analysis of Cyproheptadine HCl was done by using UV-Visible spectrophotometer & Drug-Excipients compatibility study was conducted by FTIR. Oil, Surfactant, & Co-surfactant were selected based on the results of a solubility study for the formulation of Nanoemulsion, while the ratio of surfactant to co-surfactant (Smix) was determined through pseudo-ternary phase diagram study. $3^2$ full Factorial Design was applied using Design Expert 13 software. Concentration of Oil ($X_1$) & Concentration of Smix ($X_2$) were chosen as independent variables, while Particle size ($Y_1$) & Zeta potential ($Y_2$) were selected as dependent variables. From the experimental design, $NE_7$ batch containing 10% Capryol 90 & 60% Smix in 3:1 ratio of Tween 80: Transcutol P exhibited Particle size 132.9 nm & Zeta potential was -10.1 mV. Nanoemulgel prepared from Optimized Nanoemulsion showed great 94.75% Drug diffusion at 7 hr & it remained consistently stable over 1 month stability study. It is concluded that Nanoemulgel of Cyproheptadine HCl was formulated successfully.

**Keywords:** Cyproheptadine HCl, Nanoemulsion, Nanoemulgel, $3^2$ full Factorial Design.

## I. INTRODUCTION OF DISEASE

- Allergies are caused by a hypersensitivity reaction of the antibody class IgE (which are located on mast cells in the tissues and basophils in the blood).
- It is an overreaction of the immune system to a normally harmless substance called as allergens and is found in dust mites, pets, pollen, insects, ticks, molds, and some medications.

➢ ALLERGIC REACTION:

- A person is exposed to an allergen by inhaling it, swallowing it, or getting on their skin. After a person is exposed, there is a sequence of events that create an allergic reaction:
- The body produces an antibody, IgE. Allergens bind to the IgE, which is attached to the mast cell, which causes the mast cells to release a variety of chemicals into the blood such as histamine. Histamine causes most of the symptoms of an allergic reaction.
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➢ **SKIN ALLERGY:**

- The immune systems of people with skin allergies are overly sensitive. Allergens can cause them to get allergic skin rashes and other ailments.
- In addition to being dry, itchy, or painful, skin rashes can also be red, swollen, bumpy, and irritating.
- Skin rashes can be caused by bacteria, viruses, allergies, and diseases like psoriasis, atopic dermatitis, and hives.

**INTRODUCTION OF NANOEMULGEL** [6, 7, 8]

➢ Nanoemulgel are emulsions, either of the W/O or O/W type, which are gelled by mixing with a gelling agent. It can also acts as controlled release drug delivery system or medication like biological active ingredient. It can deliver both hydrophilic and hydrophobic drugs due to the presence of both aqueous & non-aqueous phase. They are commonly used due to their biocompatibility, biodegradability and high drug loading capacity.

**ADVANTAGES OF NANOEMULGEL**

➢ Nanoemulgel provides large surface area and free energy which make an efficient delivery system.

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- It shows better penetration of drug because the nano-sized particles can easily enter by the rough skin surface.
- The ability to resist First-pass metabolism.
- Effectiveness for a managed and long-term drug delivery system has been proven.
- Appropriate for self-medication.
- Patient accepts it quickly.
- It is safe on transdermal application due to its non-toxic nature.

**DISADVANTAGES OF NANOEMULGEL**

- Nanoemulgel stability is affected by environmental factor like pH and temperature.
- Bubbles formed during emulgel formulation.

**MECHANISM OF NANOEMULGEL** [10, 11]

- Nanoemulgel is work to improve permeability and drug retention while also providing a controlled release medication delivery technology.
- The formulation is made up of Oils and Surfactants, either alone or in combination with a Co-surfactant, which serves as an intrinsic permeation enhancer and gelling agent, thereby increasing permeability by improving the formulation's adhesion to the skin.

**EXPERIMENTAL WORK:**

**MATERIAL & METHOD** [6, 7, 8, 9, 10, 11]

**PREPARATION OF NANOEMULSION:**

- The high speed homogenization technique will be used to create the Cyproheptadine HCl loaded Nanoemulsion. Due to the hydrophobic nature of the drug dissolved in oil phase. Mix Oil, Surfactant and Co-surfactant by using magnetic stirrer. Mix Water drop wise into Oil phase with continuous stirring until a clear and uniform emulsion was observed. The prepared emulsion was placed in a sonicated for 10 min. The clear Emulsion was carried out to a high speed homogenization at 10,000 rpm for 15-20 min. The same process was carried out for all bathes of Emulsion. The prepared Emulsion converts into the Nanoemulsion.

**PREPARATION OF NANOEMULGEL:**

- Carbopol is commonly used as a gelling agent in semi-solid pharmaceutical formulations at concentrations between 0.5% - 2%. The production of Nanoemulgel in this study was done using Carbopol 934. Triethanolamine (TEA) was added for pH adjusting in range of 6 to 6.5 for compatibility to skin.

**Experimental design:**

The 3-level complete Factorial Design was used to examine how two significant independent factors affected the batches of Nanoemulgel. Concentration of Oil ($X_1$) & Concentration of Smix ($X_2$) were chosen as independent variables, while Particle size ($Y_1$) & Zeta potential ($Y_2$) were selected as dependent variables. Nine formulations in all were created using the $3^2$ complete Factorial Design.

A statistical model representing the interaction effect and polynomial terms are as follows:

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Here, Y is the response, b0 is the arithmetic mean response of the nine batches, $b_1$ is known as the estimated co-efficient of $X_1$ variable, and $b_2$ is of variable $X_2$. $X_1$ and $X_2$ are the main effects, which show the changing its value from high to low at once, affects the overall result. $X_1X_2$ represents the interaction effect on the response, whereas $X_1^2$ and $X_2^2$ show nonlinearity in the results.

**$3^2$ Full factorial design:**

The results of 9 experimental batches as per the $3^2$ Factorial Design were put in Table 1. By employing the statistical DESIGN EXPERT, the mathematical co-relation between factors and responses were established. For this, firstly, the data of the experiment were fitted to the suitable model. As per the various criteria of regression analysis, the software and ANOVA (Analysis of variance) select the appropriate model by which one can forecast the significance of the model at 5% of the level, a quadratic & linear model was chosen for the responses based on low PRESS value which concluded the requisite fitting of the model. Particle size ($Y_1$) (from 132.9 to 218.7 nm) and Zeta potential ($Y_2$) (from -3.91 to -13.5 mV). The data indicates that the Particle size & Zeta potential which depends on the chosen factors. It represents the outcome of the analysis of variance (ANOVA), which was employed to identify the insignificant factors.

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**Table 1- $3^2$ Factorial design batches of Nanoemulsion**

| Batch no. | Concentration of oil (%) ($X_{1)}$ | | Concentration of Smix (%) ($X_{2)}$ | |
|---|---|---|---|---|
| | Coded value | Actual value | Coded value | Actual value |
| $NE_1$ | -1 | 10 | -1 | 50 |
| $NE_2$ | 0 | 15 | -1 | 50 |
| $NE_3$ | +1 | 20 | -1 | 50 |
| $NE_4$ | -1 | 10 | 0 | 55 |
| $NE_5$ | 0 | 15 | 0 | 55 |
| $NE_6$ | +1 | 20 | 0 | 55 |
| $NE_7$ | -1 | 10 | +1 | 60 |
| $NE_8$ | 0 | 15 | +1 | 60 |
| $NE_9$ | +1 | 20 | +1 | 60 |

**EVALUATION PARAMETERS:** [8, 9, 10, 11, 12]

**Evaluation parameters of Nanoemulsion**

- **pH: -** A digital pH meter will be used. All values are observed at room temperature. All values found within pH range 6-7.
- **% Transmittance: -** A UV spectrophotometer was used to measure the transmittance percentage in order to assess transparency. Each nanoemulsion formulation was 100 times diluted with distilled water. The transmittance percentage was determined at 650 nm in a UV Visible spectrophotometer using water as blank.
- **Determination of Particle size, PDI and Zeta potential: -** The Malvern instruments, which operates on the basis of the light scattering approach, assessed the assessment of particle size, PDI and zeta potential. Ideal range of particle size of nanoemulsion between 10-500 nm, PDI between 0-1 and zeta potential between -30 to +30 mV. Nanoemulsion was mixed diluted with water in 1:9 v/v and then vortexes.
- **Centrifugation study: -** Nanoemulsion was centrifuged at 3500 rpm at 30 minutes to assess whether any kind of phase separation occurred.

**Evaluation parameters of Nanoemulgel:**

- **Physical appearance: -** Nanoemulgel was visually examined for colour, homogeneity and consistency.
- **pH:-** A digital pH meter will be used. All values are observed at room temperature. All values found within pH range 6-7.
- **Viscosity: -** Viscosity of nanoemulgel was measured by Brookfield viscometer using spindle no 64. Nanoemulgel was placed within the beaker and spindle was dipped into it and amount of viscosity was measured.
- **Spreadability: -** The equipment used to check Spreadability consisting wooden block and slide. Here known quantity of Nanoemulgel was placed on a fixed glass slide and movable glass slide with a pan attached was put over the fixed one. The maximum weights at which the gel was spread for 7.5 cm apart from the original place between two glass slides were calculated as per following equation.

$$S = (M * D)/T$$

- Here, S= Spreadability in g.cm/s
- M= mass
- T= time
- D= distance (7.5 cm)

- **Extrudability: -** Nanoemulgel was filled into collapsible tube. The amount of weight in grams, required to extrude a 0.5 cm ribbon of gel from the tube within a 10 second time period was utilized to assess the formulation's extrudability.

It is measured by using specific formula:
Extrudability= applied weight to extrude the gel from tube (gm) / Area ($cm^2$)

- **Drug content: -** 1 gm of Nanoemulgel was taken and dissolved into a 10 ml methanol by sonication. From the prepared solution 1 ml was taken and diluted with methanol. Then, the absorbance was taken at 286 nm using a UV spectrophotometer against methanol as blank.
- **In-vitro drug release study: -** In-vitro drug release study of Nanoemulgel was done by Franz-diffusion cell. Franz-diffusion cell contains donor compartment and receptor compartment. Receptor compartment was filled with pH 6.8 phosphate buffer and it was

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under continuous stirring and 32±1ºC temperature was maintained. Membrane was clamped between donor and receptor compartment of franz-diffusion cell. 1 gm of Nanoemulgel was administered onto the membrane. 1 ml of sample was taken from receptor compartment at regular interval and volume was made up with the equal volume of pH 6.8 phosphate buffer for maintenance of sink condition. Then concentration of Cyproheptadine HCl in each sample was determined by using UV-Visible spectrophotometer at 284 nm.

- **Stability Study:** One month stability study of Cyproheptadine HCl Nanoemulgel was carried out under accelerated condition (40±2ºC & 75±5% relative humidity). Nanoemulgel was evaluated for different parameters.

## II. RESULT AND DISCUSSION:

- **EVALUATION DATA OF FORMULATIONS**

**Table 2- Evaluation data of Nanoemulsion**

| Formulation Code | Particle size | PDI | % transmittance | Zeta Potential | pH | Centrifugation Study |
|---|---|---|---|---|---|---|
| **$NE_1$** | 185.4 | 0.467 | 94.59 | -13.5 | 6.2 | No phase separation |
| **$NE_2$** | 208.7 | 0.380 | 92.34 | -8.93 | 6.3 | No phase separation |
| **$NE_3$** | 218.2 | 0.490 | 91.07 | -4.78 | 5.8 | No phase separation |
| **$NE_4$** | 147.1 | 0.350 | 96.10 | -10.5 | 6.4 | No phase separation |
| **$NE_5$** | 158.8 | 0.228 | 93.49 | -5.14 | 6.2 | No phase separation |
| **$NE_6$** | 169.5 | 0.307 | 92.79 | -4.66 | 6.1 | No phase separation |
| **$NE_7$** | **132.9** | **0.267** | **97.68** | **-10.1** | **6.3** | No phase separation |
| **$NE_8$** | 154.1 | 0.244 | 95.20 | -9.74 | 6.3 | No phase separation |
| **$NE_9$** | 165.7 | 0.740 | 93.90 | -3.91 | 6.2 | No phase separation |

**Table 3- Evaluation parameters of Nanoemulgel with Stability study**

| Sr. no. | Evaluation parameter | Initial | After one month |
|---|---|---|---|
| **1** | Colour | White | White |
| **2** | Homogeneity | Excellent | Excellent |
| **3** | Consistency | Good | Good |
| **4** | pH | 6.20 | 6.26 |
| **5** | Viscosity (cps) | 8227 | 8232 |
| **6** | Spreadability (cm) | 5.7 | 5.4 |
| **7** | Extrudability | 15.20 gm/$cm^2$ | 15.07 gm/$cm^2$ |
| **8** | % Drug content | 99.23% | 98.85% |
| **9** | % Drug diffusion at 7 hr | 94.75 | 93.33 |

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**Effect of independent variable on Particle size ($Y_1$):**

The multiple regression analysis for $Y_1$ response was done by quadratic model using Design Expert 13. The Positive sign in $X_1$ suggested that particle size will increase, when increase oil value. That means amount of oil is direct relation with response $Y_1$. The negative sign in $X_2$ suggested that particle size will decrease with increasing Smix value. That means amount of Smix is inverse relation with response $Y_1$. Model p-value is 0.0024 which was less than 0.05 that indicates model is significant with $R^2$ value 0.9921. The equation generated as per the following;

Full model: $Y1= 161.178 + 14.6667X_1 + (-26.6)\ X_2 + (-1.85224E\text{-}14)\ X_1X_2 + (-4.06667)\ X_1^2 + 19.0333X_2^2$

Reduced model: $Y1= 161.178 + 14.6667X_1 + (-26.6)\ X_2 + 19.0333X_2^2$

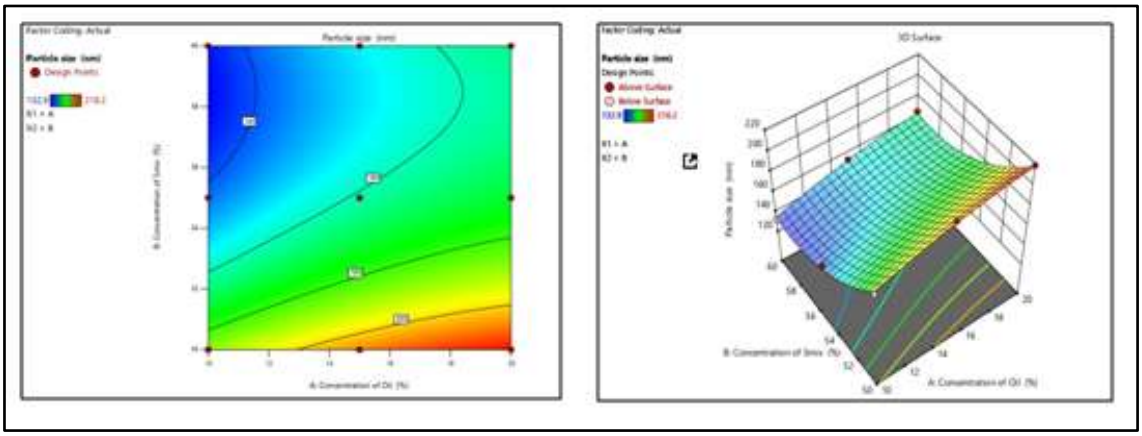

**Figure 1- Contour plot and response plot for Particle size (Y1)**

**Effect of independent variable on Zeta potential ($Y_2$):**

The multiple regression analysis for $Y_2$ response was done by linear model using Design Expert 13. The positive sign in $X_1$ suggest that zeta potential will increase, when increase oil value. That means amount of oil is direct relation with response $Y_2$. The positive sign in $X_2$ suggest that zeta potential will increase with increasing Smix value. That means amount of Smix is direct relation with response $Y_2$. P-value is 0.0070 which was less than 0.05 that indicates model is significant with $R^2$ value 0.8090.The equation generated as per the following;

Full model: $Y2= -7.91778+ 3.45833X_1 + 0.576667X_2$

Reduced model: $Y2= -7.91778+ 3.45833X_1$

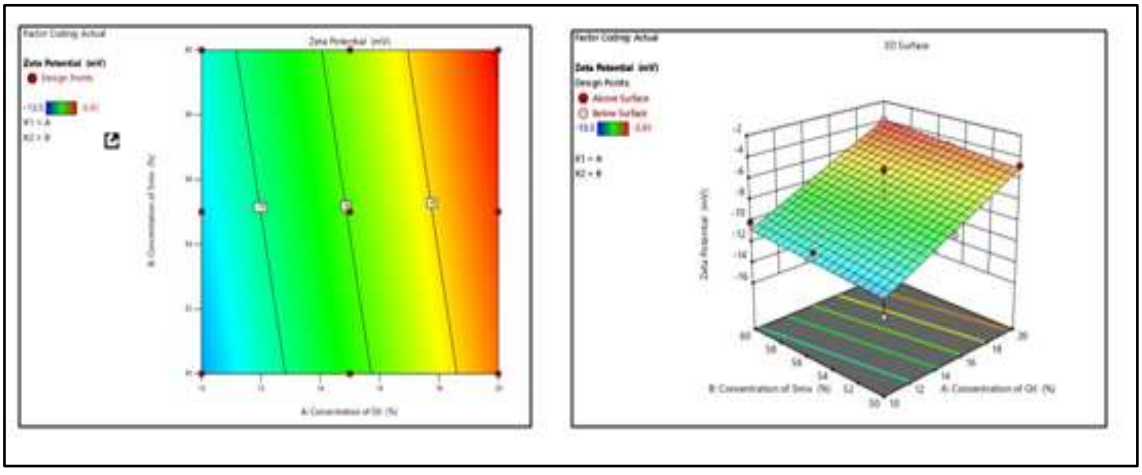

**Figure 2- Contour plot and response plot for Zeta potential (Y2)**

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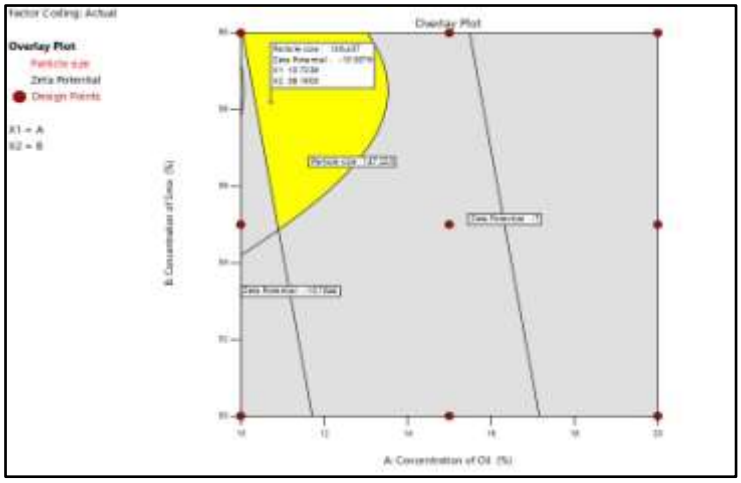


**Figure 3-Overlay plot**

**OPTIMIZATION OF FORMULATION:**

- $NE_7$ was selected as an optimized batch for preparing Nanoemulgel, as it showed particle size with 132.9 nm and Zeta potential with -10.1 mV.

**COMPARISON OF IN VITRO DIFFUSION STUDY INITIAL AND AFTER 1 MONTH**

The comparison for in vitro diffusion study of Cyproheptadine HCl Nanoemulgel was carried out. Comparison of % drug diffusion data initial and after 1 month & graph of obtain data will be given in table no 4.

**Table 4 – Comparison of drug diffusion study of Nanoemulgel**

| Sr No | Time (min) | % Drug diffusion (Initial) | % Drug diffusion (After 1 month) |
|---|---|---|---|
| 1 | 30 | 14.85 | 12.06 |
| 2 | 60 | 29.70 | 28.36 |
| 3 | 120 | 44.91 | 43.29 |
| 4 | 180 | 57.07 | 56.69 |
| 5 | 240 | 69.14 | 68.02 |
| 6 | 300 | 78.32 | 76.52 |
| 7 | 360 | 85.63 | 84.03 |
| 8 | 420 | 94.75 | 93.33 |

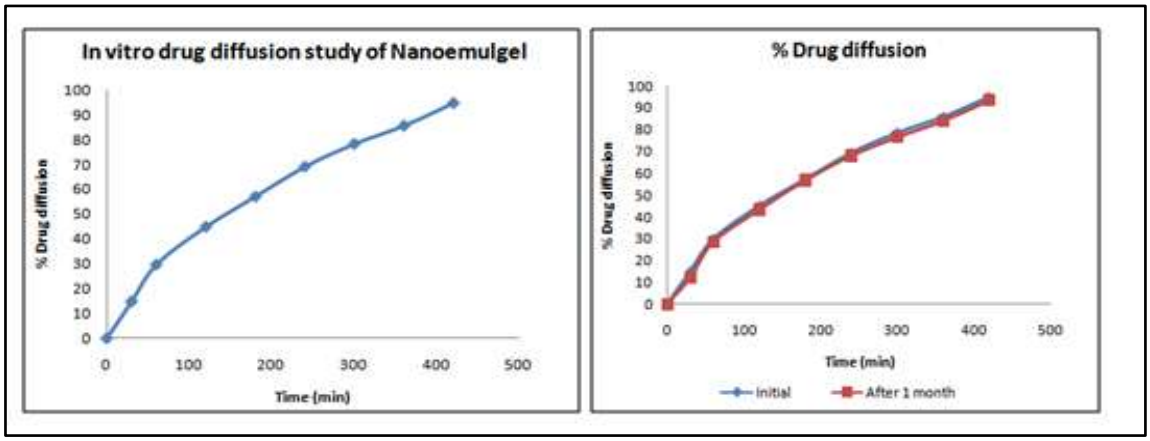


**Figure 4- (A) In Vitro drug diffusion of Nanoemulgel (B) Comparison of in vitro drug diffusion profile of Nanoemulgel before and after 1 month**

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## III. CONCLUSION:

In this present research work aimed to formulate evaluated a Nanoemulgel for the treatment of allergic reactions. Cyproheptadine HCl is a selective antihistamine drug which is used to treatment of allergic reaction. Spectrometric analysis of Cyproheptadine HCl in methanol and phosphate buffer pH 6.8 was done by using UV Spectrometer and λ max was obtained at 286 and 284 nm respectively. Identification of drug and drug-excipients compatibility study was conducted by Fourier Transform Infrared Spectroscopy (FTTR). In solubility study, Capryol 90, Tween 80 and Transcutol P demonstrated highest solubility of Cyproheptadine HCl. So they are selected for the Nanoemulsion preparation. Pseudo Ternary phase diagrams for different Smix rations were constructed. In which, Smix 3:1 showed highest Nanoemulsion region compared to other. So it was selected for preparation of Nanoemulsion. $3^2$ full factorial Design was applied for optimization of Cyproheptadine HCl Nanoemulsion. In which, Concentration of Oil ($X_1$) and Concentration of Smix ($X_2$) were chosen as independent variables, while Particle size ($Y_1$) and Zeta potential ($Y_2$) were selected as dependent variables. Nine batches were formulated and statistical analysis of dependent variables was done. Check point batch ($NE_{10}$) was formulated and evaluated. All experimental responses were near to predicted responses. So model was valid. Optimized $NE_7$ batch was incorporated into gel using 1% carbopol 934. Prepared Nanoemulgel has excellent homogeneity, good consistency, skin compatible with 6.20 pH, 8227 cps viscosity, 5.7 cm spreadability, 15.20 gm/cm$^2$ extrudability and 99.23 % drug content. In vitro drug diffusion study was carried out by using Franz diffusion cell and it demonstrated 94.75% drug release at 7 hr. Stability study of Nanoemulgel was conducted for one month. After one month Nanoemulgel is stable. In Comparison with Conventional gel of Cyproheptadine HCl, Nanoemulgel show highest drug diffusion at 7 hr. So, it is concluded that prepared Nanoemulgel can be effectively used for treatment of allergic reaction.

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