FORMULATION AND EVALUATION OF HALOBETASOL PROPIONATE LOADED LIPOSOMAL GEL FOR TOPICAL APPLICATION

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ABSTRACT

The current study work's goal and purpose are to create and assess a liposomal gel for the topical delivery of halobetasol. Lecithin and cholesterol were used as the liposomal carriers for the Halobetasol gel, and Carbopol was used as the gel-forming agent. Initial API characterization was performed, and it was successful. The liposomal formulation was optimized using the full factorial method. Lecithin and cholesterol were shown to have a substantial impact on particle size and entrapment effectiveness. Validation of design model done and found satisfactory. The final optimized formulation O1 was then used to make gel, and the O1 formulation underwent a stability study. After an acceptable one-month stability investigation, O1 was chosen as the batch to optimize.

Key Words: Halobetasol, Liposomal gel

1. INTRODUCTION

Introduction of Drug Delivery System

Introduction of Topical drug delivery system [1, 2]

Topical drug delivery methods are focused on delivering therapeutic substances locally through the skin to address cutaneous disorders. Typically, these devices are employed to treat localised skin infections. The formulations come in a variety of forms, including solid, semisolid, and liquid. Drug absorption through the skin is increased if the drug ingredient in the solution has a favourable lipid/water partition coefficient and if it is a non-electrolyte. Although dermatological medicines come in a variety of formulations and consistencies, semisolid dosage forms are the most widely used.

Dermal products that are applied topically are divided into those that have local and systemic effects. When alternative routes of drug administration fail, as shown in Figure .1, these systems are typically utilised for local skin infections.

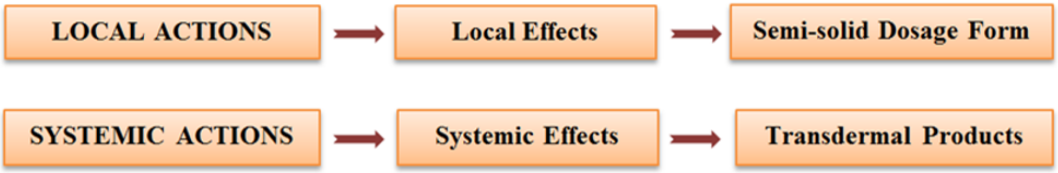

Figure 1 Local and Systemic Actions

Low-dose drug molecules that are effectively applied topically to a small area of the body are effective. In its natural state, stratum corneum contains 40% lipids, 40% protein, and just 20% water. The drug's lipophilic nature makes it best suited for topical distribution, and its transport is facilitated by dissolving into the lipids found between the cells of the stratum corneum. However, because the stratum corneum layer contains little water, it is challenging to transport hydrophilic medications there. Through "pores" or holes of the hair follicles and sebaceous glands, which prevent medication absorption, these molecules are taken up by the skin.

For topical drug delivery systems to achieve and maintain constant, systemic therapeutic levels during the course of treatment, percutaneous absorption is the best factor to take into account. The medication that is passively absorbed through the skin must be sufficiently lipophilic and have a molecular weight under 500 Da.

Drugs applied dermally reach the area with the highest concentration possible while having fewer adverse effects, a higher bioavailability, and better patient compliance. The skin is one of the most important and easily accessible organs on the human body for topical medication administration. The stratum corneum acts as a significant penetration barrier to allow medications to enter and pass through the skin. However, this layer is picky about the delivery method.

Topical Drug Classification System (TCS) [3]

TCS offers a paradigm for categorising topical medicinal items based on qualitative and quantitative content. As shown in figure 1.2, topical medication products are divided into 4 types.

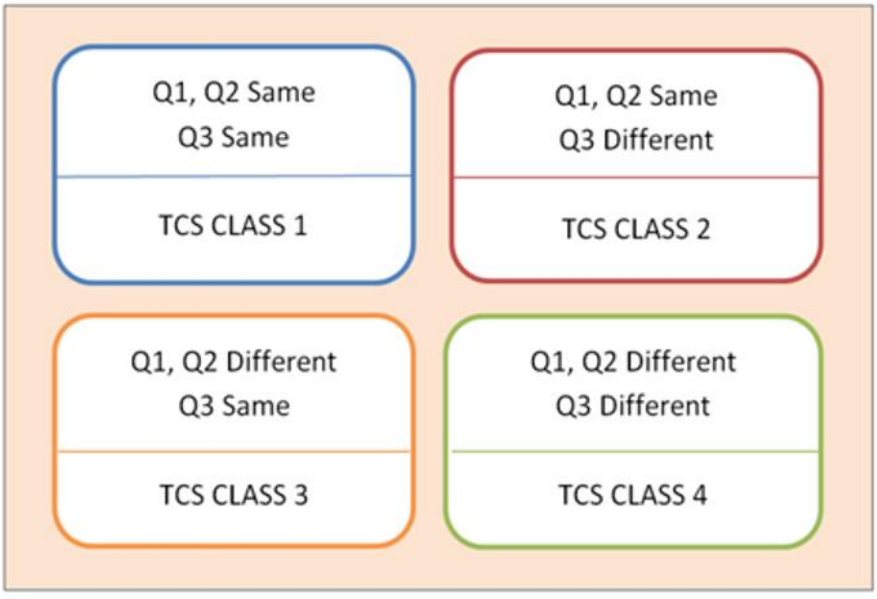

Figure :2 Classification of Topical Drug Products Based on Qualitative & Quantitative Composition

Advantages of topical drug delivery systems [4]

- Steer clear of first-pass metabolism.
- Simple to apply and convenient to use.
- It is simple to stop taking the drugs.
- Site-specific drug delivery that is selective.
- The stomach-intestinal compatibility will not occur.
- Offers drug use with a limited therapeutic window and short biological half-life.
- Improved patient adherence.
- Self-medication.
- It offers efficacy at low doses and with ongoing drug ingestion.
- Reduces risk and variability in drug levels.
- A wider application scope than other routes.
- Drug distribution at a specified location

Disadvantages of topical drug delivery systems [4]

- Potential for localised skin irritation at the application location.
- Contact dermatitis brought on by a medication is possible.
- Some medications with low skin permeability are challenging to absorb through the skin.
- Larger drug particles are more difficult to penetrate.
- The potential for allergic responses.
- Drugs can be employed for activity with very low plasma concentrations.

2. MATERIALS AND METHODS :

Sr. No.	Name of Material	Role	Sources of Material
1.	Halobetasol Propionate	API	TRC, Ahmedabad
2.	Carbopol 941	Gel forming Polymer	Lubrizol, Mumbai.
3	Soya lecithin Egg yolk lecithin	Liposomal Carrier	Lubrizole, Mumbai.
4	Cholesterol	Liposomal Carrier	Lubrizole, Mumbai.
5	Methyl Paraben	Preservative	Gangwal Chemicals, Ahmedabad.
6	Propyl Paraben	Preservative	Gangwal Chemicals, Ahmedabad.

Pre-Formulation Studies

Characterization of Drug

Organoleptic Characteristics:

Colour, odour of Drug was characterized and recorded using descriptive terminology.

Flow Properties

Bulk density and tapped density

An accurately weighed quantity of the blend (W), was carefully poured into the100 ml graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus) the density apparatus was set for 100 taps and after that the volume (V_f) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.

Bulk density = W/ V_0 Tapped density = W/ V_f.....(i)

Compressibility index (CI) / Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

% Carr's index = (Tapped Density – Bulk Density ÷ Tapped Density) × 100...(ii)

Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷ Bulk Density) .....(iii)

Angle of repose

Angle of repose of powder was determined by the funnel method. Accurately weight powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ= h/r.....(iv)

Drug-Excipients Compatibility Study By FTIR

The potassium bromide (KBr) pellet method was used to record the Fourier transform infrared spectra of the drug's final formulation and moisture-free powdered sample on an IR spectrophotometer. It was discovered that the spectrum's range was 600 to 4000 cm-1. Comparing the characteristic peaks of various functional groups to the reported standard peak.

Calibration Curve of Halobetasol

Determination of λmax of Halobetasol

The drug solution of 10µg/ml in buffer medium was scanned in the range of 200 to 400 nm using UV spectrometer.

Calibration Curve of Halobetasol

Spectrophotometric measurement of halobetasol was performed at 240 nm using a methanolic phosphate buffer. A precise 10 mg dose of the medication was weighed, dissolved in 20 ml of methanol, and then made up to a volume of 100 ml with 7.4 phosphate buffer. 1 ml was collected from this stock solution and diluted to 7.4 phosphate buffer. From this stock solution, many dilutions were created to produce a concentration range of 5–25 g/ml. The calibration curve was obtained by plotting the absorbance at 240 nm against a blank of 10% methanolic phosphate buffer.

Preparation of Halobetasol Liposomes

Thin Film Hydration Method

- ✓ Liposomes were prepared by thin film method.
- ✓ Lecithin, cholesterol, and 10 mg Drug were dissolved in 5 ml chloroform methanol mixture (1:1).
- ✓ The quantities of lecithin and cholesterol were changed to enhance loading drug in liposomes.
- ✓ Then the mixture was evaporated in a rotary at 150 rpm for 30 min.
- ✓ The thin film formed in the round-bottomed flask was hydrated with phosphate buffer saline for 30 min.
- ✓ Glass ball was used for dispersion of liposome

- **Formulation table for trial batches for screening of materials**

Batch Code	Halobetasol (mg)	Soya Lecithin (mg)	Egg yolk Lecithin (mg)	Cholesterol (mg)	Vortex Time (min)
T1	100.0	-	200.0	100.0	30.0
T2	100.0	-	400.0	200.0	30.0
T3	100.0	200.0	-	100.0	30.0
T4	100.0	400.0	-	200.0	30.0

Table 1 Formulation table for factorial batches

Batch Code	Halobetasol (mg)	Lecithin (mg)	Cholesterol (mg)	Vortex Time (min)
F1	100.0	200.0	100.0	30.0
F2	100.0	200.0	200.0	30.0
F3	100.0	200.0	300.0	30.0
F4	100.0	400.0	100.0	30.0
F5	100.0	400.0	200.0	30.0

F6	100.0	400.0	300.0	30.0
F7	100.0	600.0	100.0	30.0
F8	100.0	600.0	200.0	30.0
F9	100.0	600.0	300.0	30.0

Evaluation of Halobetasol Liposomes

Particle Size Determination

Using a microscope approach, the average diameter and polydispersity index (PDI) of liposomes were calculated.

Entrapment efficiency

Halobetasol liposome was separated from unentrapped drug using centrifugation method. Liposomes were centrifuged at 20000 rpm for 1 hr at controlled temperature. Supernatant containing unentrapped halobetasol was withdrawn and measured UV spectrophotometrically at 240 nm against methanol. The amount of halobetasol entrapped in liposome was determined as follow;

$$\textbf{EE (\%) = [(Cd -Cf)/Cd] 100……..(v)}$$

Where Cd is concentration detected of total halobetasol and Cf is concentration of free drug. The entrapment efficiency was obtained by repeating the experiment in triplicate and the values were expressed as mean standard deviation.

Drug Release Study

Franz diffusion cell with a cellulose membrane was used to determine the release rate of drug from different liposomal formulations. The cellulose (molecular weight G12000) membrane was first hydrated in distilled water solution at 25ºC for 24 hours. The membrane was then fixed between the donor and receptor compartments of the cell. The receptor chamber contained 22 mL of methanol-phosphate buffer pH 7.4 (2:1) and was continually stirred using a magnet stirrer (300 rpm) at 37ºC. Two ml of the sample was withdrawn from each batch at definite time intervals (0.5, 1, 2, 3, 4, 5, 6, 8) and replaced with the same amount of phosphate buffer to maintain skin condition. The release concentrations of drug were determined by UV spectrophotometer at 240 nm. The results were plotted as cumulative released drug percent versus time.

Drug Release Kinetic Study

By fitting on kinetic models, including frequently used models like zero order, first order, Hixson-Crowell, Korsmeyer-Peppas, and Higuchi models, drug release from liposomal formulations was explained.

Zeta potential (ζ) determination

Zetameter was used to determine the surface of the drug-charged vesicles. Average zeta potential and charge on the liposome were obtained after an analysis period of 60s.

Surface morphology (SEM)

Their SEM was examined and captured by a scanning electron microscope after final preparation.

Preparation of liposomal gel

A PBS buffer solution (pH 7.4) was gradually supplemented with carbomer 940 (1%), which was continuously stirred with a paddle stirrer. Methyl paraben was added in the amount of 0.2% to preserve the gel. To achieve a neutral pH and clarify the gels, triethanolamine was then added. The gels were given time to swell while being moderately stirred after the entire amount of solid material had been added.

Evaluation of Liposomal Gel

Physical Examination

The prepared F9G gel formulation's colour, homogeneity, consistency, and spredability were all visually assessed. Utilising natural light, the clarity was assessed, and all macroscopic analyses were evaluated in comparison to carbopol.

Measurement of pH

With the use of a digital pH metre, the pH of several gel compositions was measured. In 100 ml of distilled water, one gramme of gel was dissolved before being let to stand for two hours. Each formulation's pH was measured three times, with the average readings being computed.

Viscosity

Using a Brookfield Viscometer, the viscosity of the produced gel was measured. The rotation rate of the gels was 1.5 revolutions per minute, and the viscosity was expressed in Cps.

Drug Content

100 mg of the gel sample was taken out and dissolved in 50 ml of phosphate buffer in a volumetric flask of 100 ml. Phosphate buffer should be used to increase the capacity to 100 ml. Filter the solution, then use a UV spectrophotometer set to 240 nm to check for drug content.

Content Uniformity

By examining the drug concentration in gel obtained from three to four distinct spots on the container, the consistency of the content was assessed. In the instance of liposomal gel, it was mixed with enough methanol to extract the medication before being examined using a UV spectrophotometer at 240 nm.

Stability of liposomal gel

For one month, the liposomal formulations were kept in the refrigerator to assess their colour, appearance, and drug concentration. Initial evaluation criteria were regarded as preliminary findings. The samples were taken out after a month, the analysis was done, and the final results were compared to the preliminary ones.

3. RESULTS & DISCUSSION

Pre-Formulation Studies

Characterization of Drug

Results of API characterization are given in below table;

Table 2 API Characterization

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Properties	Colour	It is white to off-white crystalline powder
2		Odour	Is is Characteristic odour
3	Flow Properties	Bulk density (g /ml)	The bulk density is 0.27 g/ml
4		Tapped density (g /ml)	The tapped density is 0.32 g/ml
5		Carr's index (%)	It is 15.6
6		Hausner's ratio	Its is 1.18
7		Angle of repose (θ°)	Its is 41.5
8	Melting Point	Capillary Method	The melting point is 214°C

Following API characterization, it was determined that using the direct compression method is preferred because the API itself has strong flow properties. The suggested formulation, however, is a liposomal gel that doesn't need any special flow characteristics. Additionally, the drug's melting point complies with the values that have been recorded.

Calibration Curve

The drug shows 240 nm λ_{max} in 10% methanolic Phosphate buffer as solvent.

Table 3 Standard calibration curve of halobetasol

Sr. No.	Concentration (µg/ml)	Average Absorbance ± SD
1.	0	0.000 ± 0.000
2.	5.0	0.167 ± 0.001
3.	10.0	0.354 ± 0.002
4.	15.0	0.531 ± 0.001
5.	20.0	0.722 ± 0.001
6.	25.0	0.876 ± 0.003

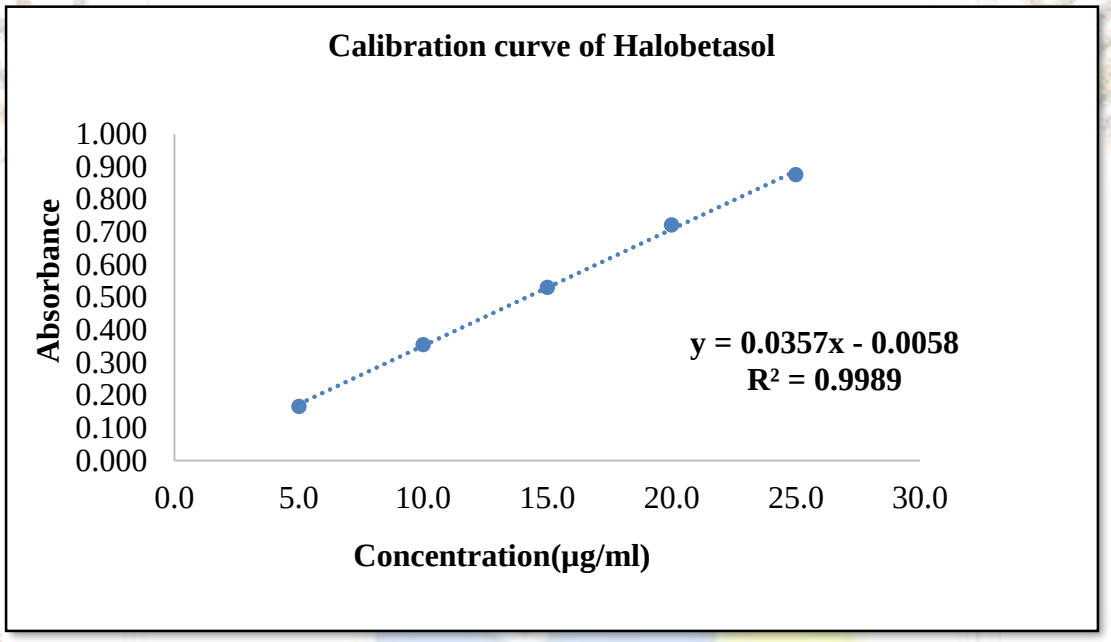

Figure 3 Standard calibration curve of halobetasol

Based on above calibration curve, it was observed that the linearity curve was achieved and R^2 was found 0.9989.

FTIR STUDY

The FTIR analysis of the formulation mixture and the pure medication is shown in the figure below. The same drug peaks can be seen in both the mixture and the pure drug spectra. The suggested excipients are therefore compatible with the medication.

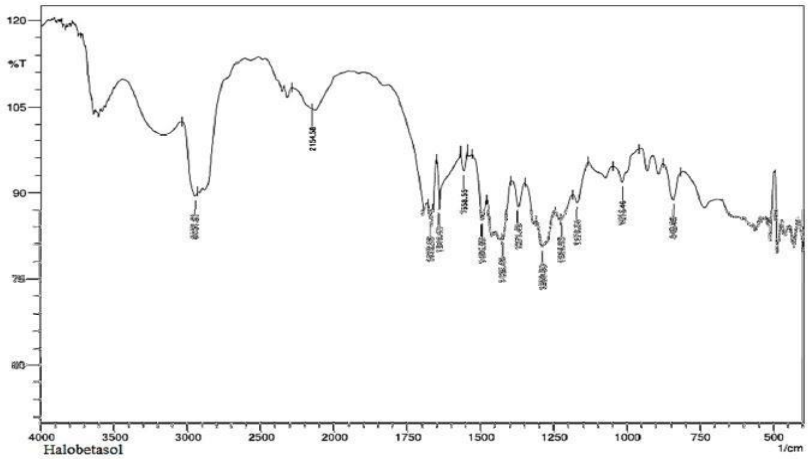

Figure 4 FTIR spectra of pure drug

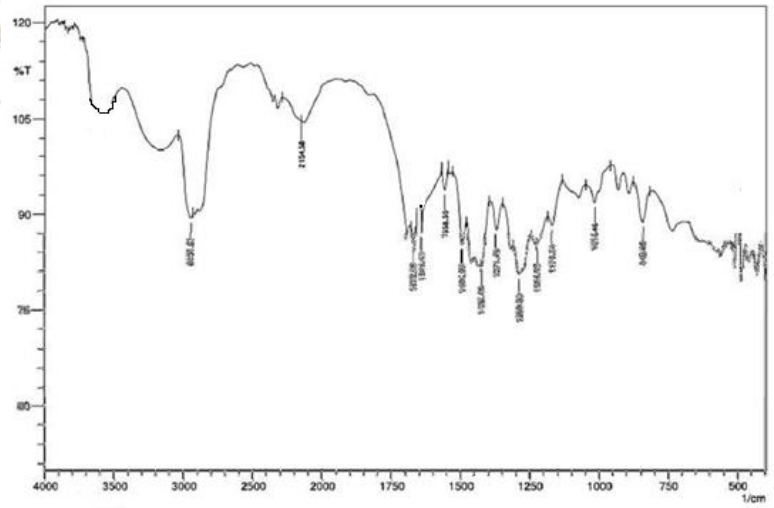

Figure 5 FTIR spectra of formulation mixture

Sr. No.	Assignment	Peak report in Pure Drug (cm^{-1})	Peak report in Physical Mixture (cm^{-1})
1	C-H stretching	1506.9	1505.2
2	C=O stretching	2154.3	2154.3
3	C=C stretching	2935.2	2934.3

Evaluation of Liposome Formulation

Evaluation of trial batch

Batch Code	Appearance of Vesicles	Particle Size (µm) ± SD	Entrapment Efficiency (%) ± SD
T1	uneven	0.20 ± 0.02	24.9 ± 1.2
T2	uneven	0.25 ± 0.03	36.3 ± 1.4
T3	Round	0.41 ± 0.02	48.1 ± 1.6
T4	Round	0.48 ± 0.04	59.6 ± 2.2

Drug Diffusion study of trial batches T1-T4

Time (hr)	T1	T2	T3	T4
0	0.0	0.0	0.0	0.0
0.5	52.1 ± 3.2	42.3 ± 4.3	39.3 ± 3.7	32.9 ± 3.4
1.0	65.3 ± 2.5	56.2 ± 3.4	48.2 ± 3.1	45.2 ± 3.1
2.0	78.4 ± 2.4	69.4 ± 3.2	59.7 ± 3.2	57.3 ± 3.0
3.0	89.5 ± 1.9	78.2 ± 2.4	68.5 ± 2.8	65.1 ± 2.7
4.0	98.3 ± 1.4	87.9 ± 2.3	77.3 ± 2.1	74.3 ± 2.5
5.0	-	99.4 ± 1.8	86.4 ± 1.9	82.5 ± 2.3
6.0	-	-	94.2 ± 1.6	88.9 ± 2.1
7.0	-	-	98.6 ± 1.4	93.1 ± 1.8
8.0	-	-	-	99.2 ± 1.6

Evaluation of factorial batches

Liposome Formulation F1-F9 was prepared using thin film hydration method. The prepared batches F1-F9 was evaluated for various parameters which are given below;

Table 4 Evaluation of F1-F9 batches

Batch Code	Appearance of Vesicles	Particle Size (µm) ± SD	Entrapment Efficiency (%) ± SD
F1	Round	0.43 ± 0.02	50.5 ± 1.6
F2	Round	0.46 ± 0.03	53.1 ± 1.4
F3	Round	0.48 ± 0.01	56.9 ± 1.3
F4	Round	0.51 ± 0.04	58.4 ± 1.8
F5	Round	0.52 ± 0.02	61.9 ± 1.7
F6	Round	0.54 ± 0.01	63.8 ± 1.3
F7	Round	0.62 ± 0.03	65.4 ± 1.2

F8	Round	0.67 ± 0.02	67.3 ± 1.3
F9	Round	0.71 ± 0.03	71.9 ± 1.2

Evaluation of F1-F9 batches was performed. The shape of vesicles is found round in all batches. The Particle size as find between 0.43 to 0.71 µm. the Entrapment efficiency was checked and found 50.5 to 71.9 % in all batches.

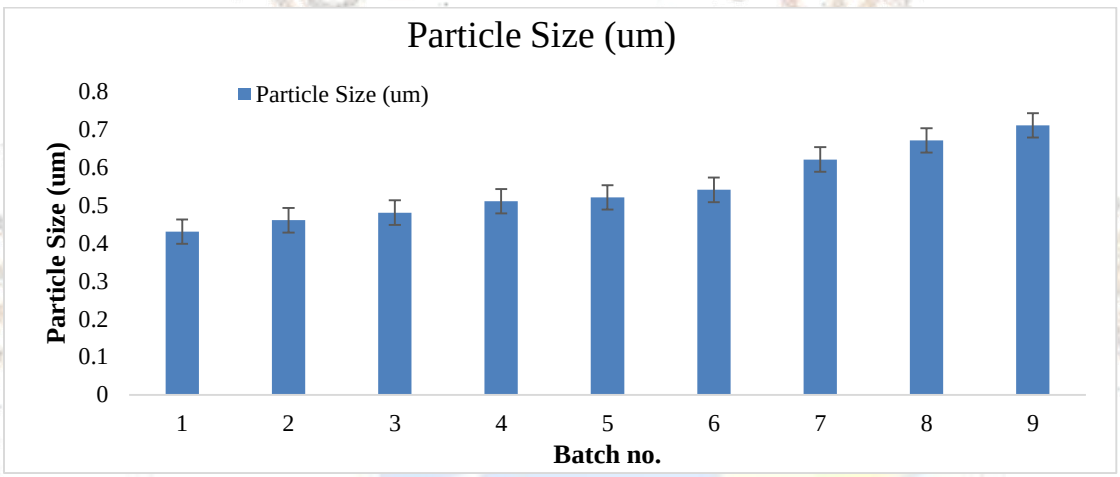

Figure 0 Particle size of F1-F9

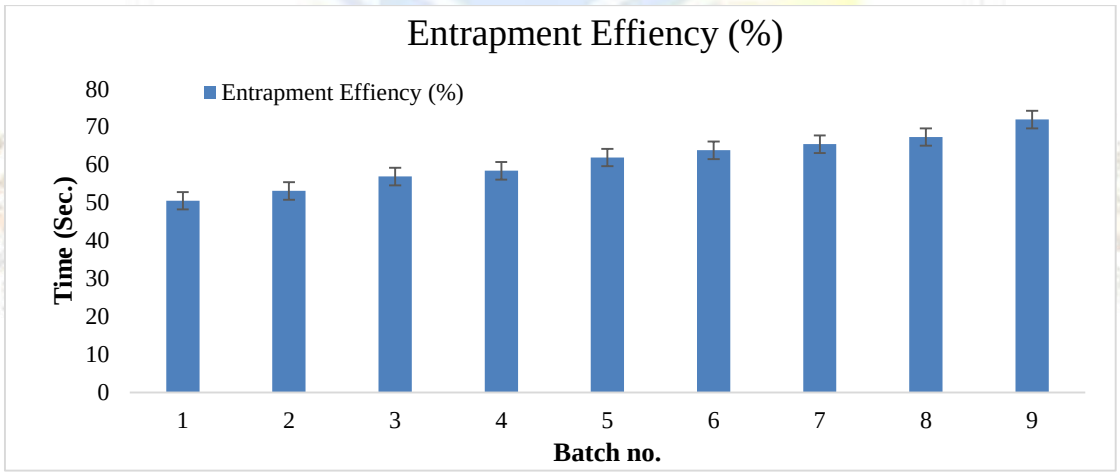

Figure 7 Entrapment Efficiency of F1-F9

The Entrapment efficiency and particle size both are increase as the amount of lecithin and cholesterol increased.

Drug Release of F1-F9 batches

Drug release study of F1-F9 batches were performed and given in below table.

Table 5 Drug release study of F1-F9

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	38.7	39.7	42.1	34.5	35.3	36.4	26.8	27.8	31.2
1	45.5	46.8	49.1	42.8	44.1	45.3	35.1	36.7	38.3
2	59.4	58.6	58.9	50.1	48.8	50.1	41.2	43.2	44.2
3	68.1	65.8	69.2	64.8	66.4	63.7	49.5	48.4	49.7
4	78.2	79.0	77.9	71.2	70.4	71.8	55.5	53.8	56.4
5	88.9	90.6	93.1	77.8	79.8	81.2	62.4	64.1	64.8
6	97.9	98.8	100.6	86.4	88.5	85.8	68.9	71.4	73.3
7	-	-	-	99.2	99.9	99.1	82.1	84.7	83.7
8	-	-	-	-	-	-	91.7	94.4	94.4

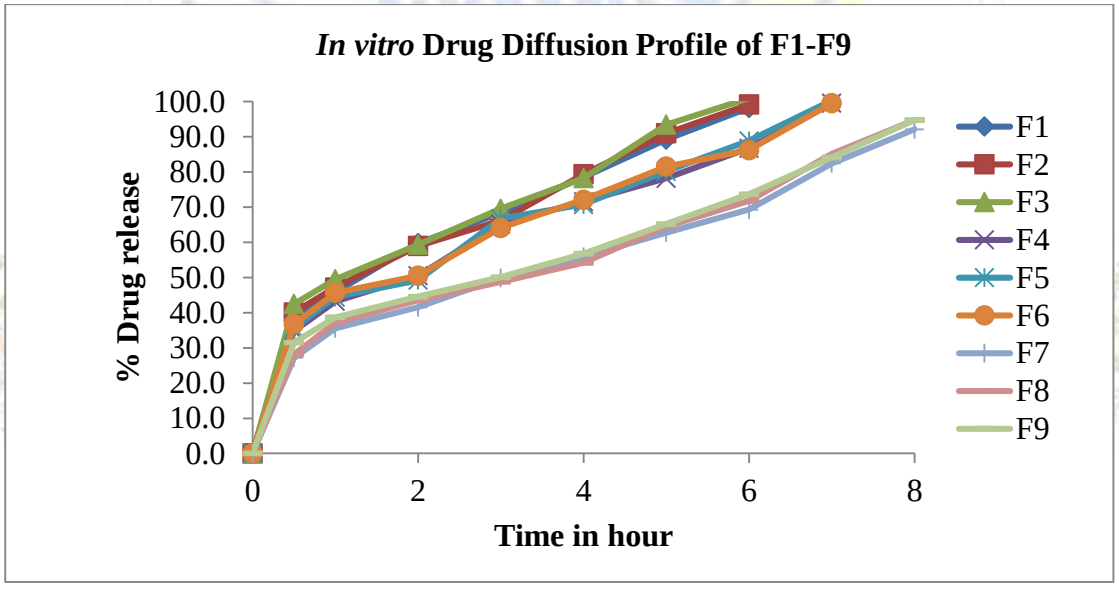

Figure 8 Drug release study of F1-F9

- **SEM of optimized formulation F9**

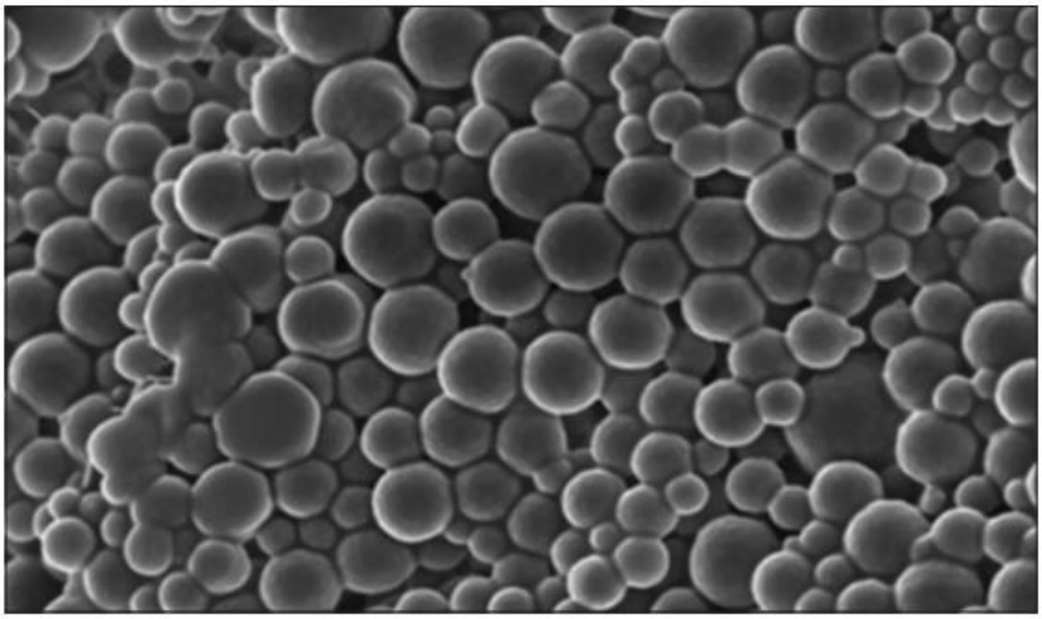

Figure 9 SEM of F9 Formulation

Table 0 Formulation table for optimized batch O1

Batch Code	Halobetasol (mg)	Lecithin (mg)	Cholesterol (mg)	Vortex Time (min)
O1	100.0	427.9	204.1	30.0

1% Carbopol used for Gel Preparation.

Evaluation of Gel formulation

For the Gel formulation, the O1 formulation was evaluated. The formulation included 1% Carbopol, and gel was prepared. The medication content and uniformity of the gel formulation's contents were assessed.

Table 7 Evaluation of F9G Gel Formulation

Batch	Appearance of gel	Texture	pH	Viscosity (cps)	Drug Content (%)	Content Uniformity (%)
O1	It is White color gel	It is Smooth	5.3 ± 0.1	1511 ± 19	99.3 ± 1.2	98.9 ± 1.1

- ✓ The macroscopic properties and attributes of the Gel formulation, including colour, homogeneity, phase separation, and consistency, were examined. The gel is translucent, has a white colour, and a smooth texture. It also smells like gel extract. The formulations were discovered to be homogenous and free of aggregates, variations, or colour intensity.
- ✓ A modest spread of time indicated that the spreadability of F7-FLZ gel was high. The distribution of gels affects their therapeutic efficacy. The produced gels must have good spredability and satisfy the optimum quality in topical application since spreading the gel aids in its uniform application to the skin. Furthermore, this is seen as a crucial element in ensuring patient adherence to therapy.

- ✓ The homogeneity of the material is one of the most important characteristics of topical formulations since it is applied to the delicate skin layers, where the gel's viscosity is key in controlling drug absorption. The optimised liposomal gel's measured viscosity was 1511 centipoises. With an increase in polymer concentration, the viscosity rises.
- ✓ Based on the aforementioned findings, it was determined that the prepared gel was deemed satisfactory. The same formulation was the subject of a one-month stability investigation.

Stability Study

Selection of Packaging Material: - The Gel type formulations were packed in Aluminum Metal Soft Tube Packaging which is cost effective and globally available packing material have a good stability during long term storage. Other packing materials are highly costly and not viable for generic product in the market. The cost of Aluminum Metal Soft Tube Packaging material is 2.4-2.5 INR per peace where other Packing materials are above 4.0 INR. Hence it is comparatively very cheap and economic.

For O1 formulation, we have selected Aluminum Metal Soft Tube Packaging and stability study performed for 1 month.

Stability study of O1formulation was performed and results are reported below;

Table 8 Stability study of F9G

O1 Batch	Appearance of gel	Texture	Drug Content (%)	Content Uniformity (%)
Initial	White color gel	Smooth	99.4 ± 0.5	98.5 ± 1.2
After 1 Month	White color gel	Smooth	99.1 ± 0.9	98.7 ± 1.6

Based on above results, the batch is found stable for 1 month. All the parameter are complying and found satisfactory.

Comparison with marketed Product

The final formulation which is liposomal gel was compared with the marketed product. The comparative results are given below. It was observed that the test product is much better as compared to the marketed product due to liposomal addition.

Table 9 Comparison with marketed product

Parameters	O1 Batch	Marketed Product
Appearance of gel	White color gel	Light Yellow color gel
Smooth	Smooth	Smooth
pH	5.4 ± 0.2	5.1 ± 0.1
Viscosity (cps)	1510 ± 18	897 ± 8
Drug Content (%)	99.4 ± 0.5	91.6± 2.1
Content Uniformity (%)	98.5 ± 1.2	90.3± 1.8
Drug release at 8 hours. (%)	94.6 ± 1.6	91.2 ± 3.2

Based on above marketed product comparison, it found that the O1 formulation was more stable and cost effective as compared to the marketed product.

4. CONCLUSION

The current study work's goal and purpose are to create and assess a liposomal gel for the topical delivery of halobetasol. Lecithin and cholesterol were used as the liposomal carriers for the Halobetasol gel, and Carbopol was used as the gel-forming agent. Initial API characterization was performed, and it was successful. The liposomal formulation was optimized using the full factorial method. Lecithin and cholesterol were shown to have a substantial impact on particle size and entrapment effectiveness. Validation of design model done and found satisfactory. The final optimized formulation O1 was then used to make gel, and the O1 formulation underwent a stability study. After an acceptable one-month stability investigation, O1 was chosen as the batch to optimize.

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