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Design and development of minoxidil-loaded nano carrier-based transdermal gel of trans-ethosomes for transdermal delivery system: *Invitro* evaluation studies

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Abstract

The present aim of the study was to develop a transdermal drug delivery system of the Nano-carrier-based Minoxidil-loaded transethosomal gel. In this study, we used Soyaphopshotidylcholine as a vesicle-forming agent and Sodium deoxycholate as a surfactant, and vesicle stabilizer as excipients. The Minoxidil transethosomes were prepared by thin film hydration technique. The prepared Minoxidil-loaded transethosomes (MTE) were evaluated and the particle size (189.83nm and 206.18nm), PDI(0.292 and 0.263), Zeta potential(-29.1mv and-28.2mv) and the entrapment efficiency (89.16±3.16 and 81.65±2.74) of MTE5 and MTE6. The MTE dispersion was further used to prepare gel, the gel base was prepared by using Carbopol, Xanthan gum, and HPMC K15. The optimized MTE-gel formulation was further evaluated, and the cumulative percentage of drug release was 98%, the 3 months stability studies show satisfactory results indicating good gel stability.

Keywords: Nano-carrier-based TDDS; Transethosomes; Minoxidil; Carbopol; HPMC k15; gels; *In-vitro* studies

1. Introduction

1.1. Introduction to Transethosomes

Transethosomes represent an innovative solution for enhancing drug delivery, especially for poorly absorbed medications. As advanced vesicular carriers, they facilitate penetration across biological barriers like the skin. A subtype of ethosomes, transethosomes are flexible, allowing them to navigate through narrow intercellular gaps.

1.2. Definition and Structure of Transethosomes

Transethosomes are nano-vesicular systems composed primarily of phospholipids, ethanol, and edge activators (like surfactants) that enhance their flexibility. With a high ethanol content, they disrupt the lipid bilayer, making the vesicles highly malleable. The addition of edge activators further increases their flexibility, enabling deeper skin penetration. This unique structure allows transethosomes to encapsulate both hydrophilic and lipophilic drugs, broadening their therapeutic applications [1].

Types of Transethosomes: Transethosomes can differ depending on their formulation components, such as phospholipid kinds, ethanol amounts, and edge activator selection. Some common kinds of transethosomes are:

- Simple Transethosomes
- Functionalized Transethosomes

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- Polymeric Transethosomes
- Hybrid Transethosomes
- Multilamellar Transethosomes.

1.3. Advantages of Transethosomes:

Enhanced Skin Penetration-Transethosomes, due to their high ethanol concentration and deformability, can penetrate deeply into the skin, bypassing the stratum corneum barrier and delivering medications directly to underlying tissues.

- **Biocompatibility**
- **Dual-Drug Encapsulation**
- **Sustained Drug Release**
- **Targeted Delivery Potential**
- **Stability Enhancement**

1.4. Disadvantages of transethosome

Transethosomes are extremely successful for transdermal and other distribution routes, although they have significant limitations [2].

- **Formulation Complexity**
- **Stability Issues**
- **Limited encapsulation efficiency**
- **High production costs**
- **Skin irritation**

The present aims to develop minoxidil-loaded transethosomes using a thin film hydration technique, further develop transethosomal gel using a gelling agent, and evaluate the transethosomal dispersion for various parameters like PDI, Zeta potential, and entrapment efficiency. The transethosomal gel formulations were evaluated for the percentage of moisture content, pH, drug content, and *In-vitro* diffusion studies that need to be performed.

2. Materials and methods

Below is the list of equipment used in the preparation and evaluation of Minoxidil-loaded transethosomal gel.

Table 1 List of equipment used in the preparation and evaluation of Minoxidil-Loaded transethosomal gel.

S.No.	Equipment	Model name
1	Analytical Balance	Sartorius, India
2	UV-Visible spectrophotometer	Shimadzu UV-1800
3	FT-IR spectrophotometer	Brukar alpha
4	Rotary evaporator	Remi Equipment Pvt.Ltd. Mumbai
5	Magnetic stirrer	Remi 1 MLH
6	pH meter	Systronics
7	Zeta sizer	Nano ZS90 Malvern zeta sizer, UK
8	Centrifuge machine	Remi Equipment Pvt.Ltd. Mumbai
9	Milli Q water purified	Millipore (India) Pvt. Ltd

Below is the list of materials used in the preparation and evaluation of Minoxidil-Loaded transethosomal gel.

Table 2 List of materials used in the preparation and evaluation of Minoxidil-Loaded transethosomal gel.

S.No.	Material Name	Use
1	Minoxidil Hydrochloride	Active pharmaceutical ingredient (API)
2	Soya Phosphatidylcholine	Vesicle forming agent
3	Sodium Deoxycholate	Surfactant and vesicle stabilizer
4	Chloroform	solvent
5	Methanol	solvent
6	Phosphate buffer saline	Hydration medium
7	Ethanol	Penetration enhancer
8	Carbopol	Gelling agent
9	Xanthan gum	Gelling agent
10	Hydroxy propyl methyl cellulose	Gelling agent
11	Methylparaben	Presravtive
12	Propyl paraben	Presravtive
13	Tri-ethanol amine	pH adjustifier
14	Propylene glycol	solvent

2.1. Determination of Minoxidil by using UV-spectroscopy method

2.1.1. Standard Stock Solution Preparation

To prepare the standard stock solution, 100mg of Minoxidil Hydrochloride was dissolved in 100 ml of methanol to obtain the desired concentration of 1000µg/ml standard stock solution. The prepared standard stock solution is pippet outed and diluted with methanol to achieve 100 stock solution. Further dilutions were made to achieve the desired concentrations and 10 solution which was then used for scanning for lambda max.

2.1.2. Determine the lambda max

Distilled methanol was taken as blank to determine the wavelength and Minoxidil Hydrochloride was scanned in the UV. The results are shown in the following graph.

2.1.3. Standard Curve of Minoxidil by UV spectrophotometer (Shimadzu-1800)

Pipette out aliquots of 1,2,3,4,5 from the stock solution. In a 10ml Volumetric flask, they are diluted with methanol to obtain the 1,2,3,4,5 ppm concentrations, respectively. Each absorbance was measured at a λmax with methanol as a blank and plotted against it to determine the value of the regression coefficient.

Preparation of Minoxidil-Loaded Transethosomes by Thin film Hydration technique

Solubilization of Components: Minoxidil Hydrochloride, Soya Phosphatidylcholine, and Sodium Deoxycholate were weighed accurately and dissolved in the solvent mixture of Chloroform and methanol of 2:1 v/v ratio

Formation of Thin Lipid Film: The prepared solution was transferred into the round bottom flask and connected to the rotary evaporator. The organic solvents were evaporated under reduced pressure at a temperature of 40-45°C until a thin, dry lipid film was formed on the inner side the flask

Hydration of Lipid Film: The Phosphate-buffered saline is prepared using 10-20% of ethanol and it was added to the round bottom flask which contains thin dry lipid film, Allowed the lipid film to get hydrated upon gentle shaking or stirring

Sonication for Vesicle Formation: After the hydration of the lipid film, a coarser dispersion was formed and sonicated for 5 min at an amplitude of 50. Through this process, we can reduce the size of the vesicles and form transethosomes.

Storage and Evaluation: After the sonication formed Minoxidil Hydrochloride transethosomes were stored in the refrigerator at 4°C and further used for the evaluation of various parameters [3]

Table 3 Formulation of Minoxidil Transethosomal Dispersion

Formulation code	**Minoxidil (mg)**	**Soya Phosphatidyl Choline (mg)**	**Cholesterol (mg)**	**Sodium Deoxycholate (mg)**	**Solvent (Chloroform: Methanol) (mL)**	**Media**	
						Phosphate Buffer 6.4 pH (mL)	Ethanol (mL)
MTE1	200	60	40	2	2:1	4.5	0.5
MTE2	200	60	40	2	2:1	4.25	0.75
MTE3	200	60	40	2	2:1	4	1
MTE4	200	70	30	2	2:1	4.5	0.5
MTE5	200	70	30	2	2:1	4.25	0.75
MTE6	200	70	30	2	2:1	4	1
MTE7	200	80	20	2	2:1	4.5	0.5
MTE8	200	80	20	2	2:1	4.25	0.75
MTE9	200	80	20	2	2:1	4	1

2.2. Evaluation of Minoxidil-Loaded Transethosomes

Particle size, Zeta potential, and PDI: Particle size characterization was done using a Zeta sizer (Nano ZS90, Malvern Instruments, UK) with the Dynamic light scattering principle. PDI indicates the size distribution (polydispersity or monodispersity) of transethosome. Zeta potential is defined as the charged particle obtained when it is present in the medium is the overall charge that the particles obtain in a particular medium. The sample was prepared by diluting 0.5 ml of the formulation with double distilled water up to 10 ml and analyzed with a Zeta sizer instrument [4] .

Entrapment efficiency: The Encapsulation Efficiency of the minoxidil-loaded TEs was determined by Ultracentrifugation followed by using UV-visible spectrophotometry. A 2ml of MTE was deposited in a centrifuge tube and it was subjected to centrifugation at a speed of 18000 rpm for 20 min at a 4 °C temperature by utilizing a cooling centrifuge. After the centrifugation, the liquid portion was isolated and analyzed by using UV-visible spectrophotometry. This test was performed to determine the amount of unentrapped drug present in the dispersion [5].

% Encapsulation Efficiency =Total amount of MTE entrapped /Total amount of Minoxidil added*100

% Drug loading =Amount of Drug entrapped / Amount of drug and lipid *100

Preparation of Minoxidil-Loaded Transethosomal gel: The Minoxidil-loaded Transethosomal gel was prepared by using various gel-forming agents such as Carbopol, Xanthan gum, and Hydroxy propyl methyl cellulose(HPMC) at different concentrations. The gel base was prepared by dissolving the gelling agent in the water and keeping it overnight in the refrigerator. At a subsequent time, preservatives such as methyl paraben and propyl paraben were dissolved in the propylene glycol and the solution was further added to the prepared gel. Afterward to neutralize the gel tri-ethanol amine was added to the gel drop-wise and till to achieve the desired pH. The homogenous minoxidil-loaded transethosomal gel was prepared and further utilized to evaluate the pH, % of moisture loss, and Percentage of drug content, and *In-vitro* drug release studies were performed[6] .

Table 4 Formulation of Minoxidil Transethosomal Gel (2% Strength)

Formulation code	Minoxidil Transethosomal Dispersion (mL)	Gelling agent	Gelling agent Concentration (%)	Tri-ethanolamine (mg)	Propylene glycol (mg)
MTG1	2.5	HPMC K15	1	5	20
MTG2	2.5	HPMC K15	1.5	5	20
MTG3	2.5	HPMC K15	2	5	20
MTG4	2.5	Carbopol 934	1	5	20
MTG5	2.5	Carbopol 934	1.5	5	20
MTG6	2.5	Carbopol 934	2	5	20
MTG7	2.5	Xanthum gum	1	5	20
MTG8	2.5	Xanthum gum	1.5	5	20
MTG9	2.5	Xanthum gum	2	5	20

2.3. Evaluation of Minoxidil-Loaded Transethosomal Gel

pH measurement: The pH of the minoxidil-loaded Transethosomal gel was determined by using a digital pH meter. 0.25 g of gel was dispersed in the 10 ml of distilled water and kept under a magnetic stirrer for 20 min at room temperature. Then by keeping the pH meter probe in the dispersed gel, the pH of the gel was determined from the display [7].

Percentage of moisture loss: The moisture loss was determined by weighing a sample of gel and noting the initial weight as (W1). The sample was then dried for 24 hours by keeping it in the desiccator. After drying, the sample was weighed again, and the final weight(W2).

Percentage of Drug content: The percentage of drug content in the minoxidil-loaded Transethosomal gel was determined by dissolving 0.5 g of gel in the suitable solvent which extracts the Minoxidil effectively. The resulting solution is then analyzed by using UV-visible spectrophotometry and measuring the specific absorbance of the wavelength of Minoxidil [8].

In-vitro diffusion studies: *In-vitro* drug release studies were performed by using a Franz diffusion cell. The gel was placed in the donor compartment and the receptor compartment was filled with Phosphate buffer solution and contained a magnetic stirrer for continuous stirring and equal distribution of the drug. The samples were collected at regular intervals diluted with suitable solvents and analyzed by using UV-visible spectrophotometry. The results were drawn in the graph by plotting the Cumulative percentage of drug release versus time [9].

Accelerated stability studies: The Stability study was conducted by keeping the optimized formulation at refrigerated conditions (5 ± 3°C) and 25 ± 2°C for 3 months. These vesicles were evaluated for pH, percentage of moisture loss and percentage of drug content, and *In-vitro* diffusion studies at an interval of 30 days for 3 months [10].

3. Results

3.1. Calibration curve of Minoxidil Hydrochloride

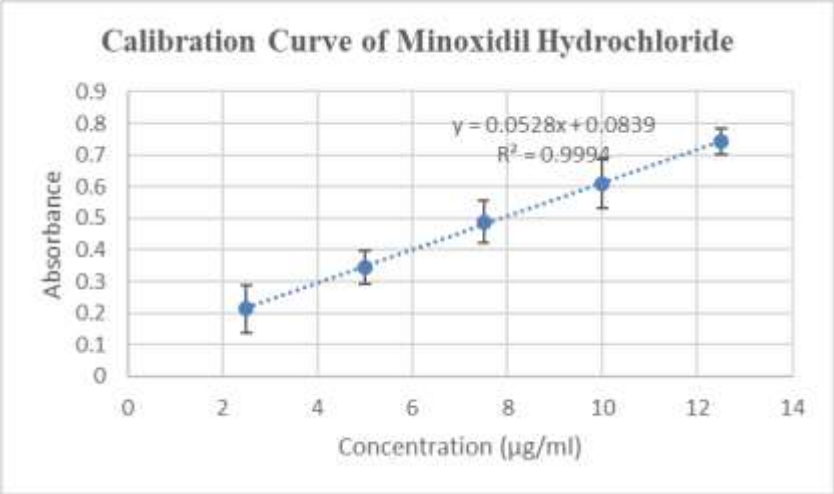

Figure 1 Calibration curve of Minoxidil Hydrochloride

Standard calibration was plotted, and the regression coefficient was found to be 0.9994.

3.2. Evaluation of Transethosomal Dispersion of Minoxidil

Table 5 Evaluation of Transethosomal Dispersion of Minoxidil

Formulation code	Vesicle Size(nm)	Zeta Potential (mv)	PDI	% Entrapment efficiency
MTE1	582.71	-21.4	0.389	69.56±4.37
MTE2	385.05	-19.1	0.291	85.51±1.84
MTE3	401.56	-26.7	0.347	74.01±2.85
MTE4	428.31	-18.4	0.461	74.84±3.85
MTE5	189.83	-29.1	0.292	89.16±3.16
MTE6	206.18	-28.2	0.263	81.65±2.74
MTE7	481.74	-14.2	0.514	66.40±4.05
MTE8	284.18	-9.6	0.431	81.84±2.55
MTE9	316.41	-10.7	0.425	75.25±3.46

Where n = 3, Mean ± SD

The results show the vesicle size, zeta potential, Polydispersity index, and Entrapment efficiency of the Minoxidil-loaded Transethosomal (MTE) formulations

3.3. Particle size of MTE 5 formulation

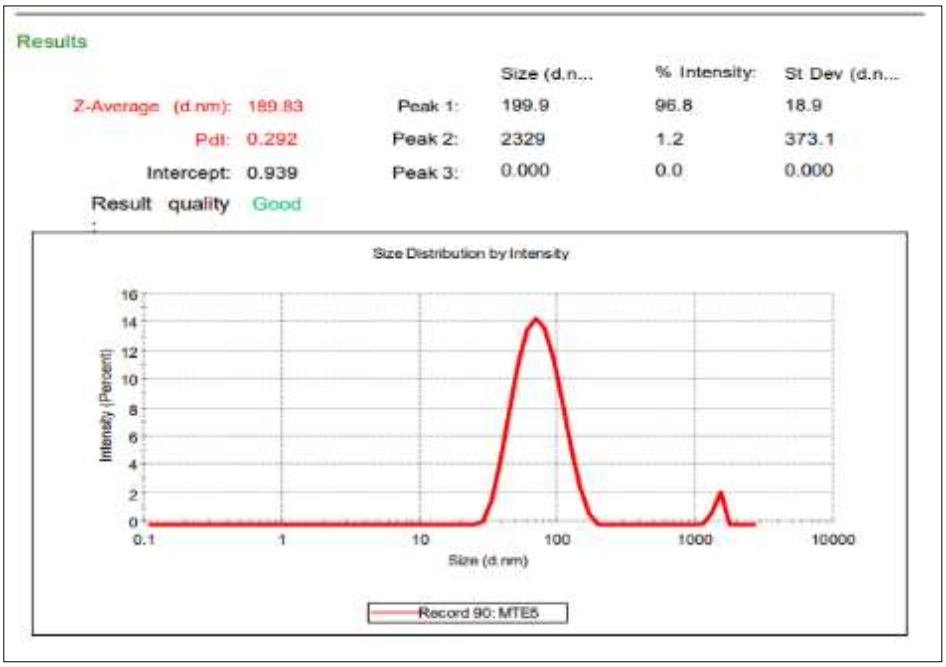

Figure 2 Particle size of MTE 5 Formulation

3.4. Zeta potential of MTE 5 formulation

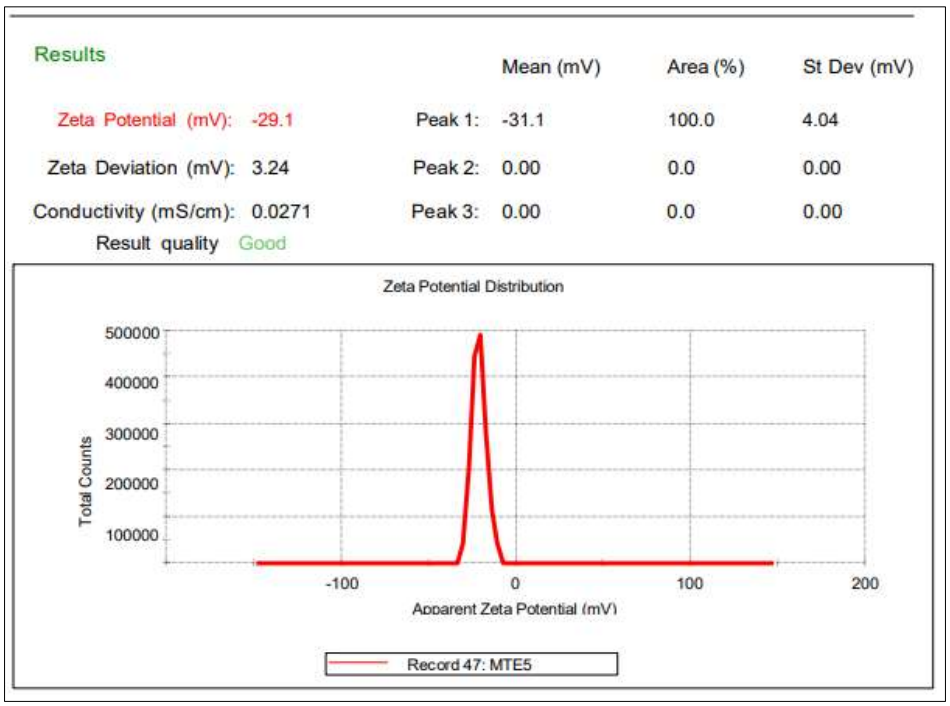

Figure 3 Zeta Potential of MTE 5 Formulation

3.5. Particle size of MTE 6 formulation

Figure 4 Particle size of MTE 6 Formulation

3.6. Zeta potential of MTE 6 formulation

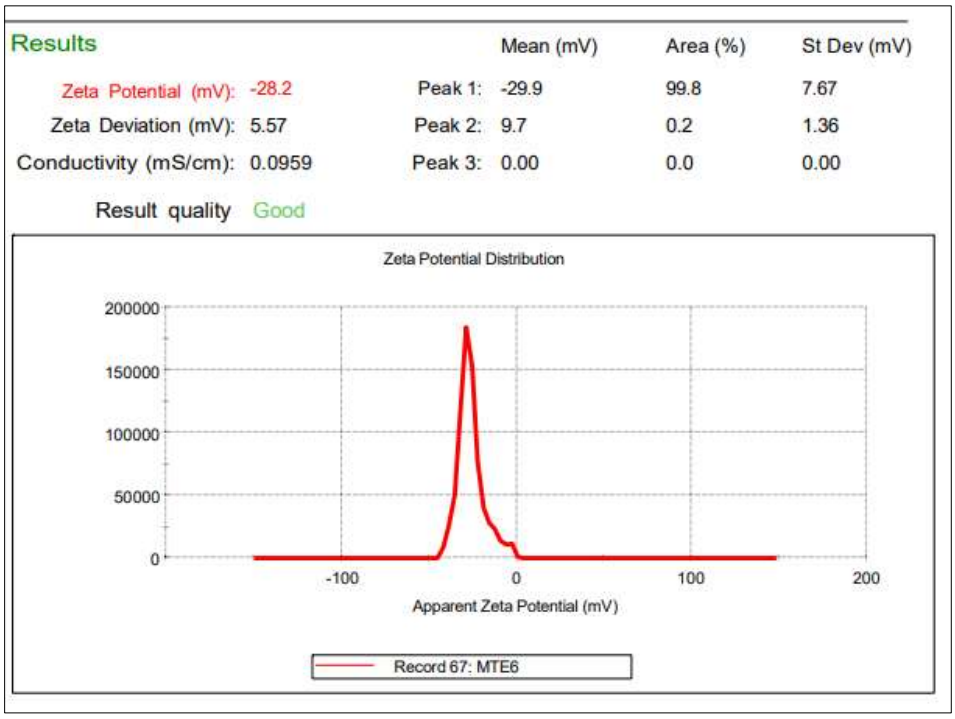

Figure 5 Zeta Potential of MTE 6 Formulation

From all formulations of MTE1 to MTE9, MTE5 shows particle size- 189.83dn m, PDI-0.292, and zeta potential - -29.1mV. MTE6 shows particle size- 206.18dn m, PDI-0.263, and zeta potential - -28.2mV.

MTE5 and MTE6 have the least particle size, good PDI value and the highest zeta potential.

3.7. Evaluation of Transethosomal Gel of Minoxidil

Table 6 Evaluation of Transethosomal Gel of Minoxidil

Formulation Code	pH	% Moisture Loss	% Drug Content
MTG1	6.1 ± 0.2	3.5 ± 0.4	98.3 ± 0.4
MTG2	6.3 ± 0.1	4.2 ± 0.5	98.9 ± 0.3
MTG3	6.0 ± 0.2	3.8 ± 0.3	99.2 ± 0.4
MTG4	6.2 ± 0.1	4.0 ± 0.4	99.0 ± 0.5
MTG5	6.6 ± 0.2	3.6 ± 0.5	98.7 ± 0.3
MTG6	6.4 ± 0.2	4.1 ± 0.3	99.4 ± 0.2
MTG7	6.5 ± 0.1	3.7 ± 0.4	99.1 ± 0.4
MTG8	6.0 ± 0.2	3.9 ± 0.5	98.8 ± 0.5
MTG9	6.3 ± 0.1	4.3 ± 0.4	99.5 ± 0.3

The pH value of each formulation, with a standard deviation (SD) indicating variability in measurements.

% Moisture Loss: The percentage of moisture loss, with SD showing the variability.

% Drug Content: The percentage of Minoxidil present in the gel formulation, with values above 98% to 99.5% and SD indicating the consistency of the drug content measurements

3.8. *In-vitro* drug diffusion studies of Minoxidil Transethosomal Gel

Table 7 Drug diffusion studies of Minoxidil Transethosomal Gel

Time (Hours	MTG1	MTG2	MTG3	MTG4	MTG5	MTG6	MTG7	MTG8	MTG9
0	0	0	0	0	0	0	0	0	0
0.5	7.41 ± 1.76	5.83 ± 1.18	3.93 ± 0.91	3.76 ± 0.83	1.72 ± 0.35	0.72 ± 0.11	68.93 ± 4.03	57.91± 2.03	47.78 ± 1.86
1	19.61 ± 2.69	14.82 ± 1.14	11.02 ± 2.33	9.96 ± 1.06	7.74 ± 1.63	4.74 ± 1.06	95.74 ± 3.47	80.25± 3.24	79.07 ± 2.67
2	31.41 ± 2.03	27.76 ± 1.99	22.63 ± 3.95	21.76 ± 1.59	13.74 ± 2.65	9.74 ± 1.32		99.09± 4.14	90.51 ± 4.33
4	49.13 ± 3.86	41.63 ± 1.25	38.94 ± 1.08	40.54 ± 2.58	20.94 ± 2.78	15.94 ± 1.69			
6	73.65 ± 4.86	58.66 ± 2.59	49.12 ± 2.62	56.77 ± 3.45	30.13 ± 1.01	26.13 ± 2.09			
8	95.45 ± 3.38	77.72 ± 2.67	57.86 ± 3.08	68.03 ± 2.26	36.98 ± 4.85	32.98 ± 1.43			
10		85.88 ± 2.25	63.74 ± 2.33	77.63 ± 5.07	53.48 ± 3.19	41.48 ± 2.16			
12		99.23 ± 3.53	76.49 ± 3.08	86.12 ± 2.53	69.88 ± 4.7	50.89 ± 2.85			
16			96.13 ± 3.94	99.03 ± 2.27	85.13 ± 4.48	73.98 ± 1.48			

24					99.57 ± 3.03	98.46 ± 2.76			

In-vitro drug diffusion studies of Minoxidil Transethosomal Gel shows that MTG6 had effective diffusion over the time period among all the other formulations.

3.9. Graph of *In-vitro* drug release study of MTE formulations from MTE1 to MTE9

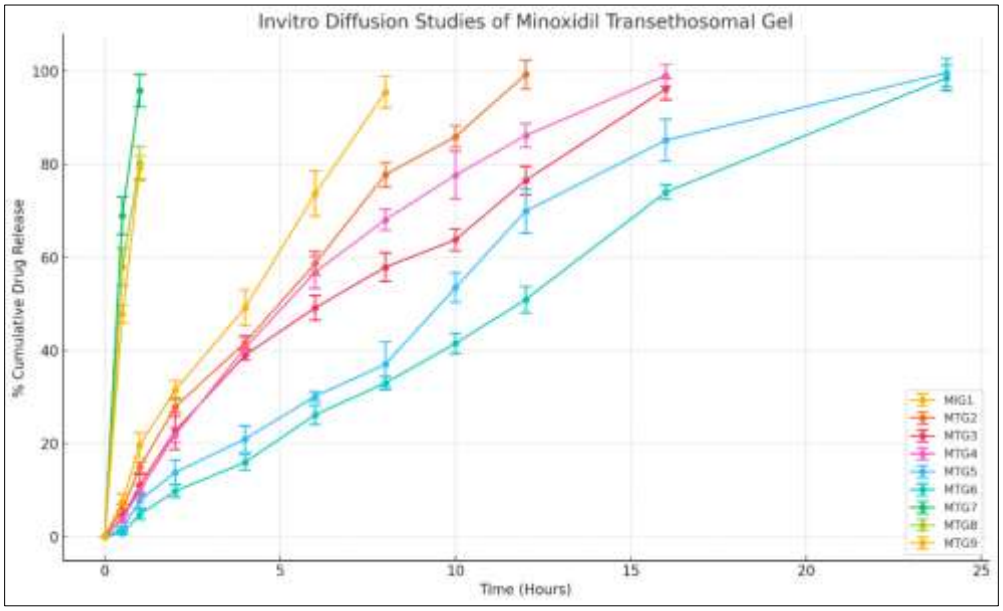

Figure 6 *In-vitro* drug release study of MTE formulations from MTE1 to MTE9

3.10. Mathematical Kinetic Modeling of MTG6 Optimized Formulation

Table 8 Kinetic Modeling of MTG6

TIME	%CDR	DR	LOG %DR	LOG %CDR	SQRT	LOG T	Wo1/3-Wt1/3
0	0	4.642	4.642	100	2	0.00	-
0.5	0.72	4.630	4.642	99.28	1.996862	0.71	-0.14267
1	4.74	4.567	4.642	95.26	1.979	1.00	0.6758
2	9.74	4.486	4.642	90.26	1.955	1.41	0.9886
4	15.94	4.381	4.642	84.06	1.925	2.00	1.2025
6	26.13	4.196	4.642	73.87	1.868	2.45	1.4171
8	32.98	4.062	4.642	67.02	1.826	2.83	1.5183
10	41.48	3.882	4.642	58.52	1.767	3.16	1.6178
12	50.89	3.662	4.642	49.11	1.691	3.46	1.7066
16	73.98	2.963	4.642	26.02	1.415	4.00	1.8691
24	98.46	1.155	4.642	1.54	0.188	4.90	1.9933

3.11. Accelerated stability studies of Minoxidil Hydrochloride Transethosomal Gel (MTG6)

Table 9 Stability studies of MTG6

Formulation Code	pH	% Moisture Loss	% Drug Content
1st Month	6.4 ± 0.4	3.5 ± 0.2	99.3 ± 0.3
2nd Month	6.4 ± 0.3	4.1 ± 0.1	99.1 ± 0.2
3rd Month	6.4 ± 0.5	5.8 ± 0.2	99.2 ± 0.2

The accelerated studies show no significant change in the parameters upon stability

3.12. *Invitro* Diffusion studies of MTG6 after 3 months of Accelerated Stability Studies

Table 10 *Invitro* Diffusion studies of MTG6

Time (Hours)	MTG6
0	0
0.5	0.81 ± 0.21
1	3.98 ± 0.96
2	10.41 ± 1.81
4	14.97 ± 1.85
6	28.73 ± 3.91
8	35.12 ± 2.41
10	42.12 ± 1.89
12	51.47 ± 3.14
16	74.18 ± 2.08
24	98.23 ± 1.36

The *In-vitro* diffusion studies results indicate that the formulation is stable upon storage

4. Conclusions

The formulation of Minoxidil-loaded transethosomal gel for transdermal drug delivery system was developed using different formulations and evaluated in various parameters. Preformulation studies were performed using UV-visible spectrophotometry and FT-IR for drug-excipient compatibility studies. The results show good compatibility among the API and excipients. Initially, Minoxidil-loaded transethosomes were prepared by using Soyaphosphotidylcholine as vesicle forming agent and Sodium Deoxycholate as a surfactant and vesicle-stabilizing agent by Rotarory Evaporation Method. The prepared transethosomes were evaluated by various parameters like Particle size, Zeta potential, Polydispersity index, and Entrapment efficiency. Among all the 9 MTE formulations, MTE5 and MTE6 are showing small particle size and good entrapment efficiency. The Minoxidil-loaded transethosomal dispersions were further used to prepare the gel by using various gelling agents such as Carbopol, Xanthan gum, and HPMC K15. The prepared gel was further evaluated in parameters like pH, Percentage of moisture of loss, Percentage of drug content, and *In-vitro* drug release studies were performed. The pH value and % Moisture Loss of each formulation were with a standard deviation (SD) indicating variability in measurements. Drug Content of percentage of Minoxidil present in the gel formulations was in the range of 98% to 99.5% and SD indicated the consistency of the drug content. The Cumulative percentage of drug release of MTE6 shows 98%release which indicates good release among all the formulations. Drug release kinetics of the MTE6 optimized formulation was taken and it follows Zero order with Anomalous fickian diffusion of drug release mechanism. Stability studies were performed on the optimized MTE6 for 3 months and there were no significant changes in the evaluation parameters which indicates good stability of the formulation.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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