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Development and Characterization of Naringenin loaded Transethsomoal gel for Anti-inflammatory activity

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ABSTRACT

The present study focuses on the development and evaluation of a naringenin-loaded transethosomal gel for enhanced topical delivery. Naringenin, a flavonoid with notable therapeutic properties, suffers from limited solubility and bioavailability, which restricts its clinical applications. To overcome these limitations, transethosomal vesicles were prepared using phospholipid, ethanol, cholesterol, and surfactants (Tween 80 and Span 60) via a thin-film hydration method. Among the ten formulations, the T6 batch demonstrated optimal entrapment efficiency (88.65%), minimal particle size (89.71 nm), and a desirable zeta potential (-10.5 mV). The optimized formulation was incorporated into a Carbopol 934-based gel and characterized for pH, viscosity, spreadability, extrudability, and drug content. In-vitro drug release studies of TEG6 high drug release profile, with 91.30% of naringenin released over 12 hours, following first-order kinetics. The gel also exhibited excellent physical stability under accelerated conditions over two months. These findings indicate that the transethosomal gel system significantly improves the solubility, stability, and sustained release of naringenin, suggesting its potential for effective topical therapy.

Keywords: *Naringenin, Transethsomoal, Gel, Anti-inflammatory*

1. INTRODUCTION

Inflammatory disorders, including dermatitis, arthritis, and other chronic conditions, continue to pose significant global health burdens [1,2]. Conventional pharmacological interventions largely rely on synthetic anti-inflammatory agents such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. While effective, their long-term use is often associated with adverse systemic effects, including gastrointestinal complications, immunosuppression, and delayed wound healing [4]. As a result, there is growing interest in safer and more effective alternatives, particularly those derived from natural sources.

Naringenin is a naturally occurring flavonoid predominantly found in citrus fruits such as grapefruits and oranges [5]. It belongs to the class of flavanones, a subclass of flavonoids, and is widely recognized for its diverse pharmacological properties [6]. Structurally characterized by its 4',5,7-trihydroxyflavanone **(Fig. 1)** framework, naringenin exhibits potent anti-inflammatory, antioxidant, antimicrobial, anticancer, and cardioprotective effects, making it a promising candidate for therapeutic development [7,8].

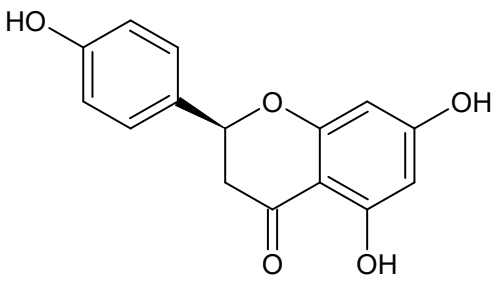

Fig. 1: Chemical structure of Naringenin.

Transethosomes combine the deformability of transfersomes and the ethanol-induced penetration-enhancing properties of ethosomes, thereby enabling deep skin penetration, improved drug loading, and sustained release [9]. In this study, we report the development and characterization of a naringenin-loaded transethosomal gel designed for topical application to combat inflammatory conditions. The formulation utilizes Carbopol 934P as the gelling agent to enhance viscosity, spreadability, and patient acceptability. The transethosomal vesicles were prepared using a thin-film hydration method and evaluated for particle size, polydispersity index (PDI), zeta potential, and % entrapment efficiency. The optimized formulation was further incorporated into a gel matrix and assessed for physicochemical properties, in-vitro drug release, release kinetics, and stability.

This work aims to offer a novel, efficient, and patient-friendly transdermal delivery system for naringenin that enhances its therapeutic index and circumvents the limitations of traditional anti-inflammatory treatments.

2. MATERIALS AND METHODS

2.1 Materials

Naringenin was procured from Sigma Aldrich Pvt. Ltd. (India). Phospholipid 90 G (PL90), sodium deoxycholate, and triethanolamine were obtained from Molychem Pvt. Ltd. (India). Ethanol and Carbopol 934P were purchased from SRL Chem Pvt. Ltd. (India). All reagents and chemicals used in this study were of analytical grade and used as received without further purification.

2.2 Preformulation study

Pre-formulation can be defined as initial phase of any product or process development where the drug's physical, chemical, and mechanical characteristics are characterized by the researchers in order to create a dosage form that is safe, stable, and effective. Preformulation studies are thus necessary to properly develop the medication delivery system by characterizing the drug. The Pre-formulation studies conducted on naringenin in this project encompass a range of parameters**.**

2.2.1 Physical properties

The physical properties were assessed and documented.

2.2.2 Melting point

The melting point of naringenin was measured using a digital instrument and capillary flow method.

2.2.3 FTIR spectroscopy

The pure drug sample was subjected to IR spectroscopy in order to identify the substance. By compressing the medication using IR grade potassium bromide and exerting 5.5 metric tonnes of pressure in a KBr press, a drug pellet was created. The pellet was mounted in the infrared chamber and examined using an FTIR spectrum analyzer (Model Mdel-8400 S, Shimadzu, Japan) 4000-450 cm^{-1} wave numbers 4000-450 cm^{-1}. The reference (B.P, 2009) was compared with the reserved peaks for various functional groups.

2.2.4 Solubility study

Solubility was determined using the pharmacopeial method. Based on naringenin solubility results in various solvents, the diffusible and dispersible fluids for drug release and pharmaceutical investigations, respectively, were chosen. One part of naringenin was added to a different part of various organic solvents like Water, ethanol, DMSO, and dimethyl formamide then the solution was shaken reciprocally at 37°C for 5 min.

2.2.5 Ultraviolet/Visible spectrophotometric method development

The calibration curve of naringenin was prepared in pH 7.4 PBS solution, to determine and quantify the naringenin during various stages of formulation development.

2.2.5.1 Absorption maxima (λ_{max}) of naringenin

UV-Visible spectrophotometer (Labindia UV 3000^{+}) was used to confirm the purity and absorption maxima of the drug. UV-Visible spectroscopy was used for the quantitative analysis of naringenin. Primary mixture (1 mg/mL) of the drug were formulated in buffer and were further diluted to obtain a ratio of 10 µg/mL. Samples were taken in 1 cm standard cuvettes and scanned in a range of 200-800 nm in a spectrophotometer to determine absorption maxima.

2.2.5.2 Standard curve of naringenin in PBS (PH 7.4)

A 1 000 µg/mL naringenin stock was made by dissolving 10 mg in 10 mL buffer, and then a 100 µg/mL secondary stock was prepared by a tenfold dilution. Working standards ranging from 10 to 100 µg/mL were generated by transferring 1–10 mL of the secondary stock into 10 mL volumetric flasks and diluting to volume with PBS. Absorbance of each standard was measured at λ_{max} (288 nm) against a PBS blank. The calibration curve were plotted absorbance versus concentration to enable quantification of naringenin in subsequent analyses [10].

2.3 Preparation Method of transethosomal Formulation

The required quantities of lipid and cholesterol were accurately weighed and dissolved in ethanol. The mixture was stirred continuously using a magnetic stirrer at 25 °C for 5 minutes to ensure complete dissolution. After thorough mixing of lipid, cholesterol, and ethanol, the surfactant was added to the solution, and the mixture was further heated at 30 °C for an additional 5 minutes. Following this, the drug was incorporated into the prepared mixture under continuous stirring. To achieve uniform vesicle size and enhance the dispersion of components, the final formulation was subjected to sonication for 5 minutes. This process facilitated the formation of well-dispersed transethosomal vesicles, as outlined in **Table 1.**

Table 1: Composition of naringenin loaded transethosomes.

Formulation code	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}
Naringenin	200	200	200	200	200	200	200	200	200	200
Soya lecithin (mg)	600	600	600	600	600	600	600	600	600	600
Tween 80	20	30	40	50	60	--	--	--	--	--
Span 60	--	--	--	--	--	20	30	40	50	60
Cholesterol	200	200	200	200	200	200	200	200	200	200
Ethanol concentration (ml)	6	6	6	6	6	6	6	6	6	6
Water (ml)	14	14	14	14	14	14	14	14	14	14

2.4 Characterization of naringenin loaded transethsomoal

2.4.1 % Entrapment efficiency

The produced transethosomes ability to entrap drug was determined using centrifugation method. A cold centrifuge was used to spin the centrifugation tubes at a speed of 15000 RPM for 30 minutes at 4°C after adding 1 ml of a drug-loaded transethosomes suspension. The unentrapped drug concentration was determined spectrophotometrically at 260 nm. The entrapment efficiency was determined using the given formula and expressed as the percentage of drugs trapped.

$$\text{EE\%} = \frac{\text{Total drug concentration} - \text{Free drug concentration}}{\text{Total drug concentration}} \times 100$$

2.4.2 Particle size

Particle size measurements of transethosomes were made using dynamic light scattering and photon correlation spectroscopy.

2.4.3 Zeta potentials

The Zeta potential of the preparation may analyse using a Zeta analyser (Litesizer Dls 501). A value of 25 mV, regardless of its polarity, may serve as the threshold that distinguishes surfaces with low charge from those with high charge. The importance of zeta potential lies in its capacity to be correlated with the stability of colloidal dispersions.

2.5 Preparation of gel

Carbopol 934 was employed as the gelling agent in the formulation. A concentration of 0.4% w/v Carbopol 934 was dissolved into distilled water under continuous stirring to ensure uniform mixing. The dispersion was then allowed to stand undisturbed for approximately 2 hours to facilitate complete swelling and gel formation. Subsequently, an appropriate preservative and triethanolamine were added to adjust the pH and complete the formation of the transethosomal (TEG1 to TEG10) gel.

2.6 Evaluation of naringenin loaded transethsomoal gel

2.6.1 Physical Evaluation

Visual inspection was used to assess the naringenin loaded transethsomoal gel physical features, clarity, occlusiveness,

washability, and organoleptic properties.

2.6.2 Determination of pH

pH testing meter was used to measure the naringenin loaded transethsomoal gel. Three duplicate readings of the data were taken, and the average value was determined.

2.6.3 Speradability

The naringenin loaded transethosomal gel speradability was assessed by measuring the diameter of a 1 g gel after 5 minutes between horizontal plates (20 x 20 cm^2). 500g was the typical weight fastened to the top plate.

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

Where **S** represents speradability, **M** is the weight tied on the upper plate (in grams), **L** is the length (in centimetres) that the glass slide moves, and **T** is the time (in seconds) taken for the movement

2.6.4 Viscosity

Using a Brookfield viscometer, the prepared naringenin loaded transethsomoal gel viscosity was measured. Using spindle number six, the reading was obtained at 100 rpm.

2.6.5 Extrudability study

The gel formulations were evaluated by filling collapsible tubes, with the formulation measured according to the weight in grams necessary to extrude a 0.8 cm ribbon of gel. [11]

2.6.6 Washability

The washability test was analyzed to assess the ease of removal of the prepared gel formulation from the skin surface. A small quantity of the gel was applied evenly to a designated area of the skin and allowed to remain for a short duration. It was then rinsed off using warm water, and the skin was examined to determine how easily the formulation washed away. This test helps evaluate the formulation's user-friendliness and suitability for topical application, particularly in terms of its residue-free removal. [12]

2.6.7 Drug content

To estimate the drug content, 1 gram of the naringenin-loaded transethosomal gel was accurately weighed and transferred into a 10 mL volumetric flask. A small quantity of methanol was added to disperse the gel, and the mixture was subjected to continuous shaking until a clear solution was obtained. The volume was then made up to 10 mL with methanol. The resulting mixture was cleared, and the drug ratio in the filtrate was quantified using UV-visible spectrophotometry by recording the absorbance at the appropriate wavelength.

2.6.8 *In-vitro* drug release study

The i*n-vitro* release study was conducted on the optimized gel (TEG1 to TEG10) encumbered with naringenin to determine the most effective formulation. This investigation used a dialysis membrane using Franz Diffusion Cell with size of 0.4 µm pore. The membrane is absorbed in a 7.4 buffer solution of phosphate for a duration of 24 hours. A quantity of 1 gram of naringenin loaded transethsomoal gel was applied to one side of the dialysis membrane. The receptor medium was filled with a 13.3ml volume of buffer solution contains phosphate at a pH of 7.4. The Franz diffusion cell was positioned on a magnetic stirrer and agitated with a magnetic bead at a stirring speed of 400 rpm. The temp is adjusted at 37±1°C. The investigation was carried out for a duration of 12 hours. At certain time intervals (0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours), a sample of 0.2 ml was obtained. The same volume was then replaced with a new solution of buffer pH 7.4. The collected samples were evaluated using a validated UV technique.

2.6.9 *In-vitro* drug release kinetics studies

An investigation was conducted on the medicine delivery from the gel by analyzing the release data using the Higuchi equation, zero-order kinetics, and first-order kinetics. Analysis of the data using the Korsmeyer Peppas model allowed for the identification of the process by which the substance is released.

The drug kinetics from pharmaceutical formulations can be described using various mathematical models.

In zero-order kinetics, the drug delivery is constant and independent of its ratio, following the equation

$C = K_o t$,

where K_o is the zero-order rate constant and t is time in hours.

In contrast, first-order kinetics implies that the release rate is dependent on the ratio of the remaining drug.

$\text{Log } C = \text{Log } C_o - Kt / 2.303$

where C_o is the initial drug concentration and K is the first-order rate constant.

Higuchi's model explains via diffusion drug delivered through matrixs.

$Qt = Kt^{1/2}$

where Qt is the delivery of drug at t time, and K is the kinetic constant.

Korsmeyer–Peppas model is used for systems with anomalous or non-Fickian drug transport.

$Mt/M\infty = Kt^n$,

where Mt is the quantity of delivered drug at t time, $M\infty$ delivery of drug in total amount, K is a kinetic constant, and n is drug release method.

2.7 Stability Study

The drug retention capacity of vesicles in a gel formulation was evaluated by subjecting the gel to various temperatures. The gel was stored in airtight vials with a capacity of 10ml at a temperature of 4 ± 2ºC and at room temp for a duration of 45 days. The drug content was measured at various time periods to ascertain the percentage.

3. RESULT AND DISCUSSION

3.1 Preformulation studies

3.1.1 Physical properties

Organoleptic evaluation revealed that the naringenin is a white to light yellow, crystalline substance with a bitter taste and characteristic aromatic odor. The organoleptic properties of naringenin as represented in **Table 2**.

Table 2: Properties of naringenin.

S. No.	Properties	Result
1.	Colour	White powder
2.	Physical form	Crystalline powder
3.	Odor	Aromatic or odorous
4.	Taste	Bitter

3.1.2 Melting point (MP) analysis

The sample analyzed in triplicate and mean was found to be **251 °C.** The mean was almost the similar as that of the reported melting point i.e., 250°C to 254°C (Drug Bank). The results of melting point are given in **Table 3**.

Table 3: MP analysis of naringenin.

Observed MP				Reported MP
MP1 ℃	MP2 ℃	MP3 ℃	Mean ℃	
250	251	251	251	250-254℃

3.1.3 Solubility study

The solubility of naringenin in dissimilar solvents was studied, namely ethanol, DMSO, Dimethyl formamide and water etc. **(Table 4 and Fig. 2).** The solubility of naringenin with water, ethanol, dimethyl foramide and DMSO were found to be 450, 2, 9.8, and 4.7 mg/mL.

Table 4: Solubility of naringenin in different solvents.

Solvent	Solubility (mg/mL)
Water	450
Ethanol	2
Dimethyl formamide	9.8
DMSO	4.7

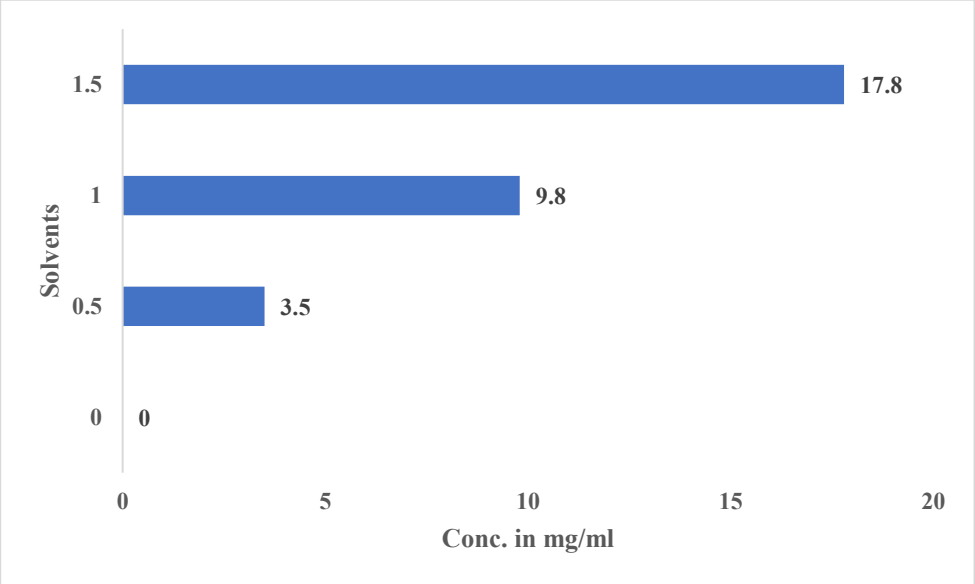

Fig. 2: Schematic representation of solubility study in different solvent system.

3.1.4 Preparation of calibration curve and Determination of λ_{max}

The spectrum of naringenin was examined and the wavelength of naringenin was found to be 260 nm which is as according to standard values**.** Then the selected wavelength of 288 nm was used for the further studies. The different ratio solution 2, 4, 6, 8, 10, 12 and 14 µg/ml were ready for the analysis. The result of the linearity curve of naringenin was found to be R^2 0.9992 (**Table 5, Fig. 3**).

Table 5: Linearity of naringenin in buffer pH 7.4 at 288 nm.

Conc. (µg/ml)	Abs.
2	0.056
4	0.124
6	0.246
8	0.383
10	0.498
12	0.678
14	0.789

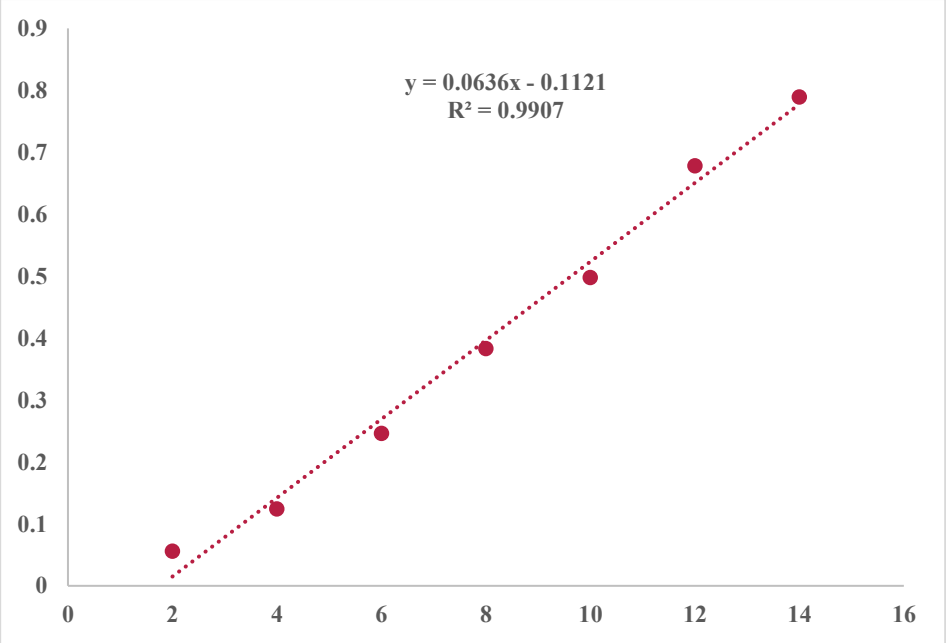

Fig. 3: Linearity curve of naringenin.

3.1.5 FT-IR spectrum of naringenin

The FTIR spectrum of naringenin was analyzed to determine the peak positions of various functional groups, confirming the drug's purity through comparison with standard references. In the FTIR spectrum of naringenin, prominent absorption bands were detected at approximately 3290 cm^{-1} and 3117 cm^{-1}, which are attributed to the O–H stretching vibrations. Additionally, a distinct and sharp peak corresponding to C=O stretching was observed at around 1626 cm^{-1}, indicating the presence of a carbonyl functional group**.**

3.2 Evaluation of naringenin loaded transethsomoal

3.2.1 Entrapment efficiency (%EE)

The % EE of all preparations ranged from 67.5 % to 88.65%. Among the formulations, Formulation T_6 exhibited the highest entrapment efficiency at 88.65% (**Table 6 and Fig. 4**). The data indicates that the entrapment efficiency of transethsomoal increases as the polymer ratio increases. Additionally, an increase in the ratio of cholesterol up to a certain amount also contributes to higher entrapment efficiency.

Table 6: Entrapment efficiency (%) of different formulations of naringenin loaded transethsomoal.

Formulation	Entrapment efficiency (%)
T_1	67.50
T_2	70.29
T_3	74.61
T_4	78.53
T_5	80.12
T_6	88.65
T_7	84.32
T_8	78.65
T_9	83.2
T_{10}	82.11

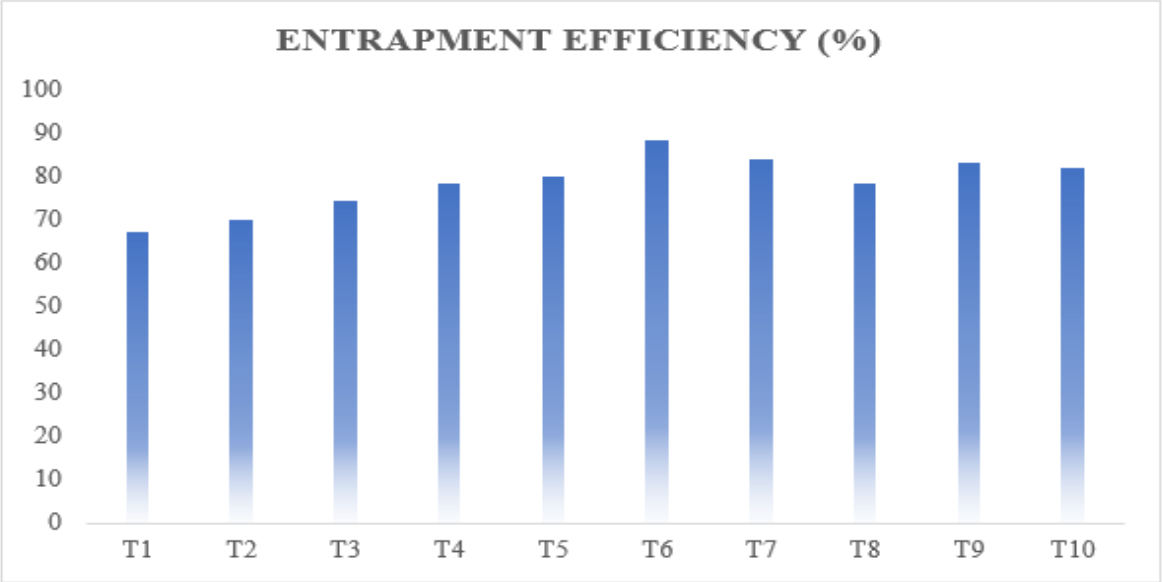

Fig. 4: Graph of % EE formulation of T_1 to T_{10}.

3.2.2 Particle size analysis and polydispersity index

An instrument Litesizer 500 used to analyse the particle size of the prepared formulation (T_1 to T_{10}) was in the range of 89.71- 202.21 nm **(Fig. 5 and Table 7)**. T_6 is the best particle size and it was found to be 89.71 nm. This result demonstrates that the prepared transethsomoal possess nano-sized particles, indicating their suitability for penetration through the skin.

The Polydispersity Index (PDI) of the transethosomes was range to be 0.26-0.45 **(Table 8 and Fig. 6),** and T_6 was found to be 0.26 indicating a uniform particle size distribution and narrow dispersion within the formulations. A PDI value equal to or less than 0.26 suggests that the sample is monodispersed.

Table 7: Different formulation particle size of naringenin loaded transethsomoal.

Formulation	Particle size (nm)
T_1	142.44
T_2	123.86
T_3	119.02
T_4	149.55
T_5	102.43
T_6	89.71
T_7	138.65
T_8	100.14
T_9	120.60
T_{10}	202.21

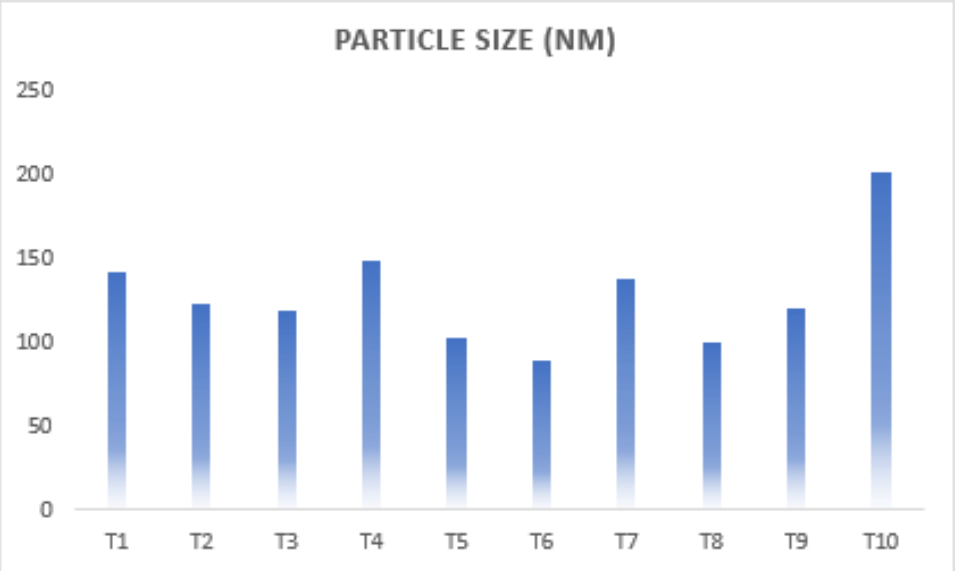

Fig. 5: Graph of particle size of formulation of T_1 to T_{10}.

Table 8: PDI of different formulations of naringenin loaded transethsomoal.

Formulation	**PDI**
T_1	0.30
T_2	0.29
T_3	0.34
T_4	0.45
T_5	0.26
T_6	0.31
T_7	0.35
T_8	0.29
T_9	0.37
T_{10}	0.36

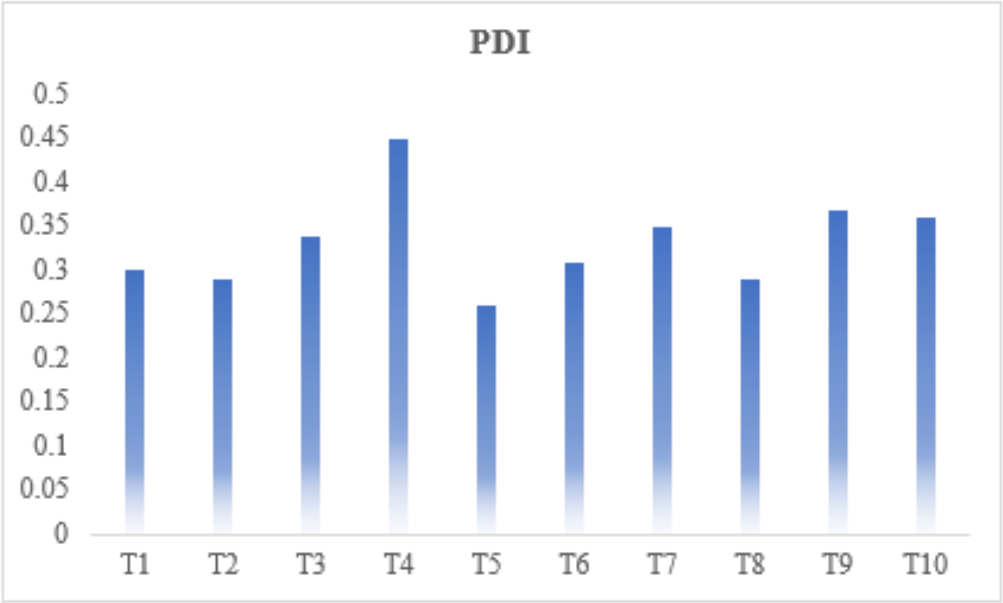

Fig. 6: Graph of PDI value of formulation of T_1 to T_{10}.

3.2.3 Zeta potential

Zeta potential is the widely utilized method generally used for the determination of the stability of colloidal dispersion. The zeta potential of T_1 to T_{10} was found to be range of -7.0 to -10.5mV **(Table 9 and Fig. 7).** An increase in zeta potential leads to enhanced repulsion between charged particles, resulting in improved stability against aggregation. In the case of the improved transethosomes preparation, T_6 formulation of zeta potential was measured to be -10.5 mV. A higher absolute value indicates a stronger electrical charge on the surface of the transethosomes, leading to robust repulsive forces among the particles and preventing their aggregation.

Table 9: Zeta potential of different formulations of naringenin loaded transethsomoal.

Formulation	Zeta potential (mV)
T_1	-7.0
T_2	-7.1
T_3	-7.6
T_4	-8.7
T_5	-9.8
T_6	-10.5
T_7	-8.8
T_8	-7.4
T_9	-7.1
T_{10}	-8.2

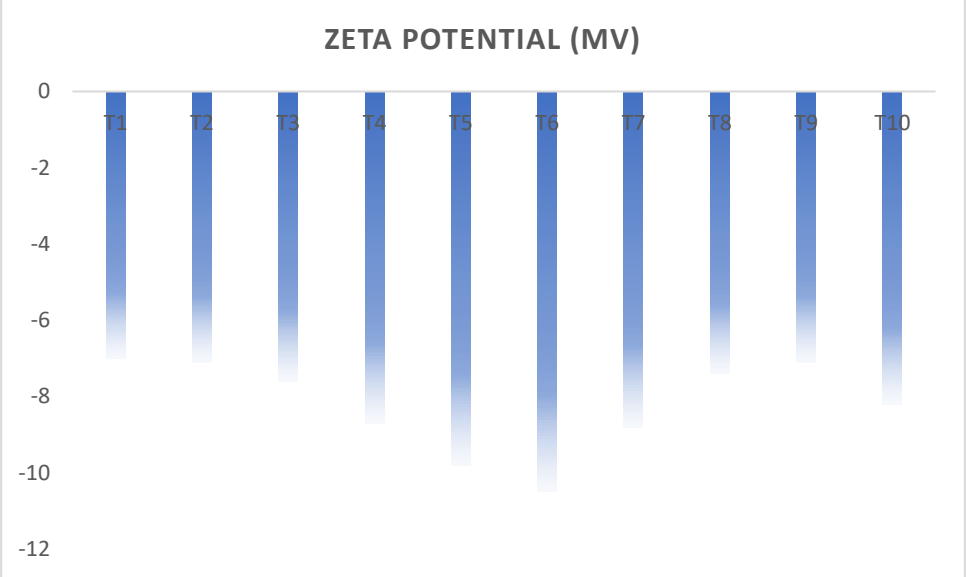

Fig. 7: Graph of zeta potential of formulation of T_1 to T_{10}.

3.3 Characterization of naringenin loaded transethsomoal gel

Out of the 10 batches of transethsomoal, the TEG6 batch exhibited the best optimal ZP, %EE, and particle size. This batch was then used to create gel formulations using carboxyvinyl polymer carbomer [Carbopol 934P (0.5%)].

3.3.1 Physical Evaluation

The physical evaluation of gel (TEG6) was shown in **Table 10.**

3.3.2 pH measurement

pH is one of the main factors in the topical gel formulation. The pH of the in-transdermal formulation should be such that it is stable at that pH while also not irritate the patient while administration. The pH gel was measured by using an electrode-based digital pH meter. The obtained pH value of gel (TEG6) was shown in **Table 10.**

3.3.3 Drug content

The drug concentration study of vesicular gel (TEG6) preparation was characterized by using a UV spectrophotometer to analyze the concentration of naringenin present in the preparation. The obtained results of the drug ratio of transethosomal were listed in **Table 10.**

3.3.4 Spreadability

The speradability was measured by using two glass slides**.** The diameter before spreading and diameter after spreading were noted and then the spreadability of the gel (TEG6) was shown in **Table 10**.

3.3.5 Washability

The formulated gel (TEG6) exhibited excellent washability properties. Upon application to the skin and subsequent washing with lukewarm water, the formulation was easily removed without leaving any visible residue. No staining or film formation was observed post-washing, indicating the gel's suitability for topical use and ease of removal during routine hygiene practices. The results of washability were shown in **Table 10**

3.3.6 Extrudability

The gel formulation (TEG6) exhibited excellent extrudability, as evidenced by the smooth and continuous flow from the syringe under moderate pressure without clogging or structural collapse. The results of extrudability were shown in **Table 10.**

3.3.7 Viscosity of gel

Brookfield viscometer with the use of spindle no. 7, speed 100 rpm the viscosity of transethosomal gel (TEG6) was determined by and the optimum viscosity is shown in **Table 10.**

Table 10: Results of naringenin-loaded transethsomoal gel.

Parameters	TEG6 (GEL)
Physical appearance	Turbid whitie
pH	6.14±0.22
Viscosity (cps)	11231±65
Drug content (%)	88.35
Exrudability	++
Spreadability (cm)	3.2
Washability	+++

Where: Excellent: +++, Good: ++,

TEG- Transethsomoal gel

3.3.8 *In vitro* drug release of naringenin-loaded transethsomoal gel

The *in-vitro* drug release was performed with the help of a dialysis membrane in the beaker. The PBS 7.4 was used as a solvent and the drug release of gel formulation was characterized by using a UV spectrophotometer to determined drug concentration (naringenin) released. The % drug release was calculated in Excel software. The obtained results of % drug release (TEG1 to TEG10) is shown in **Fig. 8 and Table 11.** The highest gel (TEG6) released 91.30% of naringenin in 12 hours by the use of the dialysis membrane method.

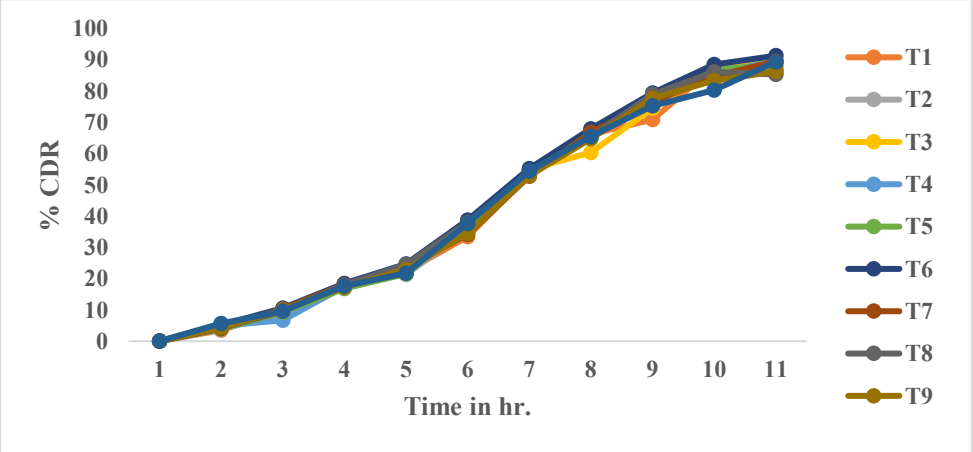

Fig. 8: *In-vitro* cumulative drug release profile of naringenin-loaded transethsomoal gel (TEG1 to TEG10 gel formulation).

Table 11: *In-vitro* cumulative drug release of naringenin-loaded transethsomoal gel (TEG1 to TEG10).

Time (Hr.)	TEG1	TEG2	TEG3	TEG4	TEG5	TEG6	TEG7	TEG8	TEG9	TEG10
0	0	0	0	0	0	0	0	0	0	0
0.5	3.5	3.8	5.1	4.9	3.9	5.12	4	4.2	4.3	5.6
1	9.8	8.8	8.7	6.7	9.2	10.51	10.2	9.5	10	9.6
1.5	17.8	18.11	18.37	17.4	16.8	18.42	18	17.9	17.2	17.65

2	22.36	21.34	22.4	23.8	21.5	24.68	23.67	24.5	22.98	21.7
3	33.4	35.6	37.8	35.8	36.9	38.76	34.13	37.9	34.4	37.6
4	53.4	54.12	55.04	54.65	53.41	55.19	52.78	53.76	52.9	54.4
6	66.12	67.12	60.32	67.12	65.21	67.86	66.8	65.3	64.7	65.4
8	70.89	78.67	74.43	76.9	78.3	79.34	76.54	78.92	77.66	75.3
10	87.65	85.89	87.9	85.89	86.9	88.47	84.65	86.12	83.4	80.31
12	86.65	87.43	90.12	89.45	88.32	91.3	89.5	85.3	86.23	89.34

TEG- Transethsomoal gel

3.3.9 *In-vitro* drug release kinetics studies

The delivery rate was established by computing the gradient of the relevant graphs, and the coefficient of determination (R^2) was also assessed of T6 gel formulation. The model fitting data for the release kinetics of naringenin loaded transethsomoal gel is presented in **Table 12** and **Fig. 9, 10, 11, and 12**. Among the different models, the first model exhibited the highest R^2 value, indicating the best fit for the data. This observation was further confirmed by plotting the percentage cumulative drug release against the time (hr), where the R^2 value ranged between 0.9961.

Table 12: Model fitting to analyzed the kinetics of drug release.

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi's (R^2)	Peppa's (R^2)	Best fitted model
Naringenin loaded transethsomoal gel	0.9293	0.9961	0.9695	0.9617	First order 0.9961

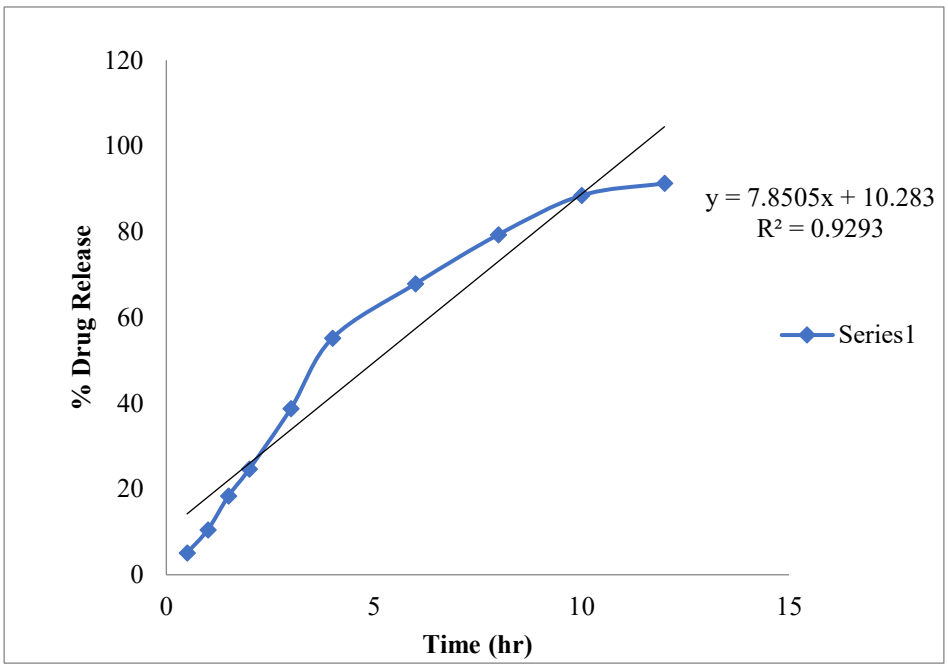

Fig. 9: Zero order plot for release kinetics of naringenin-loaded transethsomoal gel.

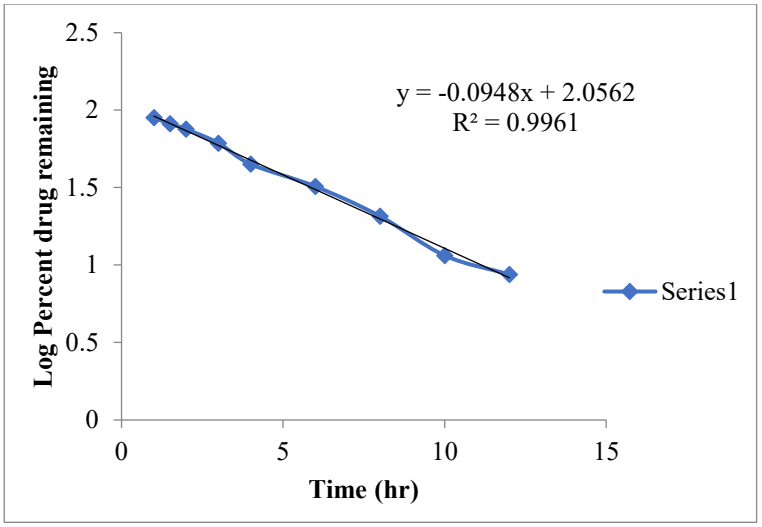

Fig. 10: First order plot for release kinetics of naringenin-loaded transethsomoal gel.

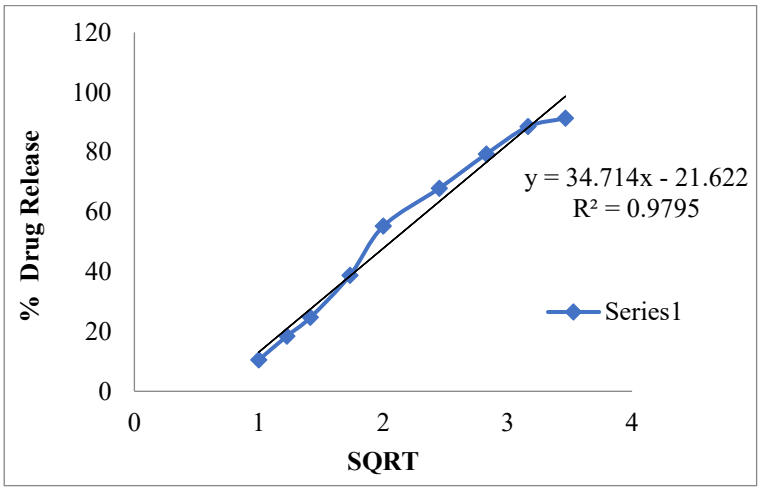

Fig. 11: Higuchi plot for release kinetics of naringenin-loaded transethsomoal gel.

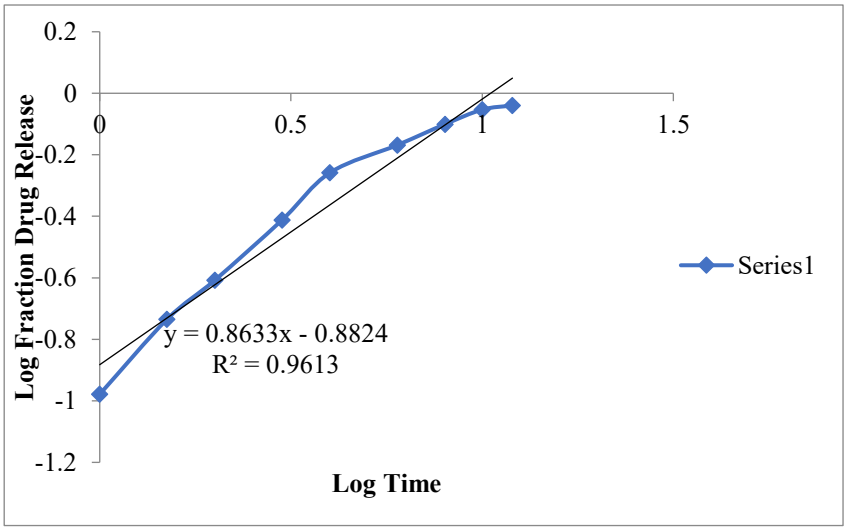

Fig. 12: Peppa's plot for release kinetics of naringenin-loaded transethsomoal gel.

3.4 Stability study

The physical stability studies of formulated gels of naringenin loaded transethosome gel were conducted for 2 months by storing them at different temperature conditions such as 4±2ºC and 25±2ºC/60±5 % RH. During the study period the gel were analysed for different parameters at specific time intervals of 1, 2 months. The gels remained clear, homogeneous and translucent during the study period of two months without undergoing phase separation **(Table 13)**.

Table 13: Results of accelerated stability studies after two months.

Evaluation parameters	Initial	1st month	2nd month
Colour	Turbid white	Turbid white	Turbid white
pH	6.2 ±0.004	6.15±0.001	6.14±0.058
Spreadability	3.1	3.0	3.2

4. CONCLUSION

The present research successfully formulated and evaluated a naringenin-loaded transethosomal gel aimed at enhancing topical drug delivery. Among the various formulations developed, the T6 batch exhibited optimal characteristics, including high entrapment efficiency (88.65%), nanoscale particle size (89.71 nm), favorable zeta potential (-10.5 mV), and uniform morphology as confirmed by TEM. Incorporation into a Carbopol 934-based gel matrix resulted in a stable, user-friendly formulation with appropriate pH, spreadability, viscosity, and excellent extrudability and washability. The in-vitro drug release study demonstrated a (TEG 6) sustained release profile with 91.30% of drug released over 12 hours, following first-order kinetics. Additionally, stability studies confirmed the physical and chemical robustness of the gel over a two-month period under different storage conditions. These findings suggest that the developed transethosomal gel offers a promising strategy for enhancing the dermal delivery and therapeutic potential of poorly soluble phytoconstituents like naringenin.

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