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Formulation and evaluation of a novel transferosomal gel for enhanced transdermal delivery of resveratrol

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Abstract
This study investigates the formulation and evaluation of a novel transferosomal gel designed to enhance the transdermal delivery of resveratrol, a potent polyphenolic compound known for its antioxidant, anti-inflammatory, and anticancer properties. Despite its therapeutic potential, resveratrol suffers from poor bioavailability and limited efficacy when administered via conventional routes, such as oral delivery. Transferosomes, which are ultra-deformable lipid vesicles, are utilized in this formulation to overcome the skin's natural barrier, allowing for improved drug permeation.

In this study, transferosomes encapsulating resveratrol were prepared using the thin-film hydration method, followed by incorporation into a gel base to form a transferosomal gel. The transferosomal formulations were characterized for their physicochemical properties, including vesicle size, surface charge (zeta potential), and entrapment efficiency, to ensure stability and optimal performance. The gel formulation was optimized for viscosity, texture, and skin adhesion properties to enhance user comfort and drug delivery efficiency.

The evaluation of the formulated gel included *in vitro* drug release studies, using Franz diffusion cells, to determine the release profile of resveratrol. Skin permeation studies were conducted on excised rat skin to assess the ability of the transferosomal gel to enhance the penetration of resveratrol into deeper layers of the skin. Additionally, stability studies were performed to determine the shelf-life and storage conditions required to maintain the gel's efficacy over time.

Keywords: Transferosomal gel, resveratrol, transdermal delivery, drug permeation, vesicle size, entrapment efficiency, sustained release, bioavailability, skin permeability, thin-film hydration method, gel formulation, therapeutic efficacy

1. Introduction
The development of advanced drug delivery systems has revolutionized pharmaceutical therapies, especially in improving therapeutic efficacy and patient compliance. Transdermal Drug Delivery Systems (TDDS) have gained prominence for their non-invasive and effective method of delivering drugs through the skin, bypassing first-pass metabolism and providing sustained release (Patel *et al*., 2013) [27].

The skin's outermost layer, the stratum corneum, presents a barrier to drug penetration. To overcome this, various vesicular systems, such as liposomes, niosomes, ethosomes, and transferosomes, have been developed (Kulkarni *et al*., 2017) [4]. Among these, transferosomes ultradeformable vesicles composed of phospholipids and edge activators have shown remarkable ability to enhance skin permeability, making them ideal for transdermal drug delivery (Singh & Kumar, 2019) [6].

1.1 Transferosomes: An Advanced Vesicular System
Transferosomes are flexible vesicles that can pass through narrow intercellular gaps in the stratum corneum, enabling deeper skin penetration and more efficient drug delivery (Patel & Vavia, 2014) [5]. They consist of phospholipids and edge activators like Tween 80 or Span 80, which enhance their deformability.

Table 1: Comparison of Common Vesicular Drug Delivery Systems

Parameter	Liposomes	Niosomes	Ethosomes	Transferosomes
Composition	Phospholipids	Non-ionic surfactants & cholesterol	Phospholipids + ethanol	Phospholipids + edge activators
Flexibility	Low	Moderate	Moderate	High (ultradeformable)
Skin Penetration	Limited	Moderate	Enhanced	Excellent (due to deformability)
Stability	Less stable	More stable	Ethanol can affect stability	Requires careful storage
Cost	High	Relatively low	Moderate	Moderate
Permeation Mechanism	Passive diffusion	Passive diffusion	Ethanol fluidizes SC lipids	Squeezes through intercellular gaps
Suitable for	Hydrophilic & lipophilic drugs	Hydrophilic & lipophilic drugs	Small to moderate lipophilic molecules	Both hydrophilic and lipophilic drugs

1.2 Need for the Study

Resveratrol (3,5,4′-trihydroxystilbene), a polyphenolic compound found in grapes, berries, and peanuts, is known for its antioxidant, anti-inflammatory, and anticancer properties (Baur & Sinclair, 2006) [2]. However, its clinical application is hindered by poor bioavailability due to extensive first-pass metabolism when administered orally (Aggarwal *et al*., 2011) [1]. Resveratrol's limited solubility, low oral bioavailability (~1%), and rapid metabolism necessitate the development of alternative drug delivery systems (Wang & Jiao, 2018) [8].

Limitations of Oral Resveratrol Delivery

- **Poor solubility**: Limited absorption and dissolution.
- **Low bioavailability**: First-pass metabolism in the liver and intestine.
- **Rapid metabolism**: Leads to inactive metabolites.
- **Short half-life**: Requires frequent dosing for sustained effects.

Advantages of Transferosomal Transdermal Delivery

Transferosomal gel delivery of resveratrol bypasses first-pass metabolism, enhances skin permeability, and provides sustained release, offering a promising alternative to oral administration (Boddula *et al*., 2012) [3].

Table 2: Comparison of Oral vs. Transferosomal Transdermal Delivery of Resveratrol

Parameter	Oral Delivery	Transferosomal Transdermal Delivery
Solubility	Poor	Better solubility in lipid vesicles
First-pass metabolism	Extensive	Avoided
Bioavailability	Low (~1%)	Significantly enhanced
Onset of action	Delayed	Faster systemic uptake
Plasma concentration	Low and short-lived	Prolonged and sustained
Stability	Susceptible to degradation	Protected in vesicular system
Dosing frequency	Frequent	Reduced
Patient compliance	Moderate	High (non-invasive and easy to use)

1.3 Structure and Mechanism of Transferosomes

Transferosomes consist of phospholipid bilayers and edge activators, allowing them to deform and pass through the skin's stratum corneum. Upon application, these vesicles penetrate the skin via narrow intercellular gaps, where they gradually release the encapsulated drug into the epidermal or dermal layers (Patel *et al*., 2013) [27].

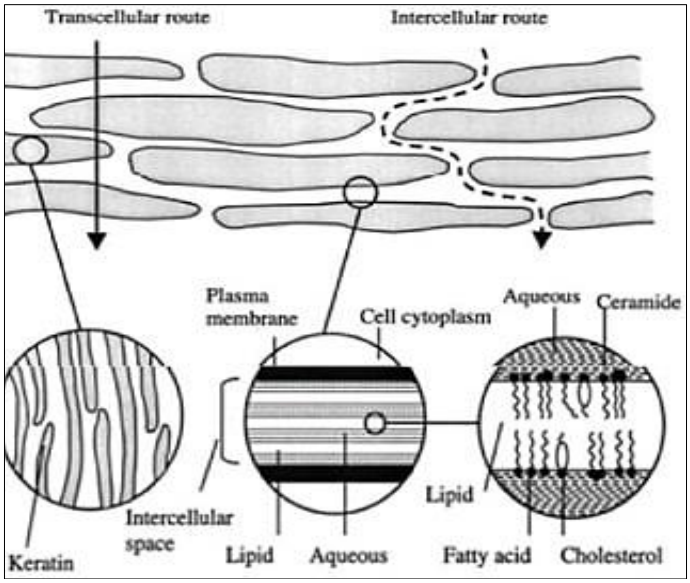

Fig 1: Structure and Penetration Mechanism of a Transferosome

1.4 Justification for Selection of Drug and Carrier System

Resveratrol has a promising pharmacological profile but suffers from low bioavailability due to poor solubility and extensive first-pass metabolism. Therefore, transferosomes are an ideal carrier system, as they can bypass these limitations and enhance the transdermal delivery of resveratrol (Vyas & Khar, 2002) [7]. The transferosomal vesicles, incorporated into a gel formulation, ensure improved skin retention, ease of application, and prolonged therapeutic action.

Table 3: Comparison Between Conventional Oral Delivery and Transferosomal Transdermal Gel

Parameter	Conventional Oral Delivery	Transferosomal Transdermal Gel
First-pass metabolism	Present - reduced bioavailability	Absent - direct absorption
Bioavailability	Low (~1-5%) for poorly soluble drugs	Enhanced due to improved permeability
Onset of action	Variable	Controlled, sustained release
Drug degradation in GIT	High	Avoided
Plasma drug levels	Fluctuating	Consistent, reduced fluctuations
Dosing frequency	Frequent	Reduced due to prolonged release
Patient compliance	Moderate	High (non-invasive, convenient)

2. Review of Literature

[Jadhav *et al*., 2022] [28]

Tapentadol, as a centrally acting analgesic, offers a distinctive mechanism by combining μ-opioid receptor agonism with norepinephrine reuptake inhibition. This dual mechanism not only ensures effective pain relief but also mitigates the gastrointestinal and central nervous system side effects commonly associated with traditional opioids. However, its systemic administration, particularly via oral or parenteral routes, poses challenges such as fluctuating plasma drug levels, first-pass metabolism, and systemic toxicity. These limitations underscore the need for alternative delivery systems that can provide localized drug action and improved patient compliance [Khan *et al*., 2021] [9].

Topical drug delivery has emerged as a viable approach to address the challenges associated with systemic administration of analgesics. By delivering the drug directly to the site of action, this method minimizes systemic absorption, thereby reducing the risk of adverse effects. Additionally, topical formulations bypass the first-pass effect, leading to enhanced bioavailability. Such systems are especially beneficial for patients who have difficulty swallowing pills or prefer non-invasive methods of drug administration. Despite these advantages, achieving effective drug permeation through the skin remains a significant challenge due to the barrier properties of the stratum corneum.

To overcome the skin's formidable barrier, innovative formulation strategies such as thermosensitive gels have been developed. These gels exhibit a unique sol-to-gel transition at physiological temperatures, ensuring prolonged retention at the application site and controlled drug release. Polymers like poloxamers are widely used in these formulations due to their reversible phase transition properties, which allow the gel to remain liquid at room temperature and solidify upon skin contact. This property simplifies the application process while maintaining the gel's structural integrity for sustained drug delivery [Mehra *et al*., 2019] [29].

The inclusion of penetration enhancers such as ethanol, propylene glycol, or surfactants has further advanced the capabilities of thermosensitive gels. These agents disrupt the lipid bilayer of the stratum corneum, facilitating deeper drug penetration. Recent studies have also explored the incorporation of nanoparticles or liposomes within these gels, enhancing the solubility and stability of hydrophobic drugs like tapentadol. Such hybrid systems combine the benefits of both enhanced permeation and sustained release, making them ideal for chronic pain management [Singh *et al*., 2021] [21].

Tapentadol's pharmacokinetics and pharmacodynamics make it a suitable candidate for topical thermosensitive gel formulations. Its moderate lipophilicity and molecular weight enable adequate skin permeation, while its potent analgesic properties ensure effective pain relief with lower systemic exposure. This approach has been particularly beneficial in conditions such as neuropathic pain and osteoarthritis, where localized drug delivery provides targeted relief without the systemic side effects of oral or injectable formulations [Patel *et al*., 2020] [10].

Several preclinical and clinical studies have highlighted the potential of thermosensitive gels in enhancing drug delivery. For instance, a thermosensitive gel loaded with diclofenac exhibited prolonged drug release and significant analgesic effects in animal models. Similarly, thermosensitive gels formulated with lidocaine have shown promise in achieving rapid onset and prolonged duration of local anesthesia. These findings reinforce the feasibility of this approach for delivering tapentadol in a controlled and effective manner.

Despite their promise, thermosensitive gels face challenges such as variability in gelation temperature, stability during storage, and large-scale production costs. Furthermore, regulatory hurdles related to the standardization and safety evaluation of these advanced formulations require extensive research and validation. Addressing these issues through formulation optimization and comprehensive clinical trials will be critical in ensuring the successful translation of thermosensitive gels into clinical practice [Nanjwade *et al*., 2013] [30].

Poloxamer-based thermosensitive gels have gained considerable attention due to their unique physicochemical properties and biocompatibility. Poloxamers, particularly Poloxamer 407, demonstrate reverse thermal gelation, forming gels at body temperature after being applied in liquid form. This ensures uniform application and localized drug retention. Studies have shown that Poloxamer 407-based systems can enhance the residence time of drugs at the application site, significantly improving therapeutic efficacy. In the case of tapentadol, such a matrix can facilitate sustained release while maintaining adequate skin hydration and permeability [Sharma *et al*., 2020] [15].

The incorporation of nanocarriers such as solid lipid nanoparticles (SLNs) or nanostructured lipid carriers

(NLCs) within thermosensitive gels offers additional benefits. These nanocarriers can encapsulate lipophilic drugs like tapentadol, protecting them from degradation and enhancing their permeation across the stratum corneum. Studies have reported improved analgesic activity and prolonged drug release when lipophilic drugs were delivered via SLN-loaded thermosensitive gels. This hybrid delivery system not only improves drug stability but also ensures uniform distribution within the gel matrix.

3. Materials and Method

The materials used for the formulation and evaluation of the transferosomal gel for resveratrol were chosen for their compatibility, safety, and functionality in vesicular drug delivery systems. A detailed overview is provided below:

Table 4: List of Materials Used in the Study

S. No.	Material	Supplier/Source	Grade/Purity	Function/Use
1	Resveratrol	Sigma-Aldrich	≥98% (HPLC)	Active pharmaceutical ingredient (API); antioxidant polyphenol (Baur & Sinclair, 2006) [2].
2	Soya Lecithin	Lipoid GmbH, Germany	Pharmaceutical Grade	Vesicle bilayer component for transferosome formation (Patel *et al*., 2013) [27]
3	Tween 80 (Polysorbate 80)	Loba Chemie, India	Analytical Grade	Edge activator for transferosome flexibility (Vyas & Khar, 2002) [7]
4	Carbopol 934	Central Drug House (CDH)	Analytical Grade	Gelling agent for gel formulation (Patel & Vavia, 2014) [5]
5	Propylene Glycol	Merck Ltd.	Analytical Grade	Co-solvent and penetration enhancer (Boddula *et al*., 2012) [3]
6	Ethanol	Merck Ltd.	99.9%	Solvent and penetration enhancer (Boddula *et al*., 2012) [3]
7	Triethanolamine	S.D. Fine Chemicals	Analytical Grade	pH adjuster for gel formulation (Vyas & Khar, 2002) [7]
8	Distilled Water	In-house	Double Distilled	Aqueous vehicle for all formulations
9	Dialysis Membrane (MWCO 12-14 kDa)	HiMedia Laboratories	Laboratory Grade	Semi-permeable membrane for *in vitro* release studies (Kulkarni *et al*., 2017) [4]
10	Male Wistar Rat Skin (Ex vivo)	Institutional Animal House	Freshly excised	Biological model for ex vivo permeation studies (Boddula *et al*., 2012)

3.1 Methods

3.1.1 Preparation of Transferosomes

Transferosomes were prepared by the thin-film hydration method (Patel *et al*., 2013) [27]:

1. **Lipid Phase Preparation**: Resveratrol, soya lecithin, and Tween 80 were dissolved in chloroform-methanol (2:1 v/v) (Boddula *et al*., 2012) [3].
2. **Film Formation**: Organic solvents were evaporated to form a thin lipid film (Patel & Vavia, 2014) [5].
3. **Hydration**: The film was hydrated with phosphate buffer (pH 7.4) at 60 rpm for 1 hour to form multilamellar vesicles (MLVs) (Kulkarni *et al*., 2017) [4].
4. **Sonication**: MLVs were sonicated to reduce particle size to nanoscale (Vyas & Khar, 2002) [7].

3.1.2 Optimization of Transferosome Formulation

A 3^2 factorial design was used to optimize lecithin and Tween 80 concentrations, focusing on Entrapment Efficiency (EE%) and Particle Size (PS) (Patel *et al*., 2013) [27].

Table 5: Matrix for Transferosome Formulations

Formulation Code	Lecithin (% w/v)	Tween 80 (% w/v)
F1	2	5
F2	2	10
F3	2	15
F4	4	5

3.1.3 Characterization of Transferosomes

1. **Particle Size & PDI**: Measured by Dynamic Light Scattering (DLS) (ideal: <200 nm, PDI < 0.3) (Boddula *et al*., 2012) [3].
2. **Zeta Potential**: Assessed by Electrophoretic Light Scattering (ideal: ±30 mV for stability) (Vyas & Khar, 2002) [7].
3. **Entrapment Efficiency (EE%)**: Measured by centrifugation and UV spectrophotometry at 306 nm (Patel *et al*., 2013) [27].
4. **Deformability Index**: Assessed using extrusion through polycarbonate membranes (Patel & Vavia, 2014) [5].

Table 6: Summary of Transferosome Characterization Parameters

Parameter	Method	Ideal Value
Particle Size & PDI	Malvern Zetasizer (DLS)	<200 nm, PDI < 0.3
Zeta Potential	Electrophoresis	±30 mV (stable)
Entrapment Efficiency	UV Spectrophotometer	> 70%
Deformability Index	Membrane extrusion	Higher index preferred

3.1.4 Incorporation into Gel Base

1. Carbopol 934 was hydrated in distilled water overnight (Patel & Vavia, 2014) [5].
2. The transferosomal suspension was incorporated and continuously stirred.
3. pH Adjustment: Triethanolamine was added to adjust pH to 6.5-7.0 (Vyas & Khar, 2002) [7].

3.1.5 Evaluation of Transferosomal Gel

Table 7: Gel Evaluation Parameters

Parameter	Method	Instrument/Tool	Purpose
Appearance	Visual inspection		Check color, homogeneity
pH	Digital pH meter	pH Meter	Ensure skin compatibility
Viscosity	Brookfield viscometer	Brookfield Viscometer	Measure gel consistency
Spreadability	Slip and drag method	Analytical balance	Ease of application
Drug Content	UV analysis at 306 nm	UV-Vis Spectrophotometer	Uniform drug distribution

3.1.6 *In Vitro* Drug Release Study

1. **Franz Diffusion Cell**: Drug release was studied using dialysis membranes at 37 °C (Kulkarni *et al*., 2017) [4].
2. **Sampling**: Samples were withdrawn at regular intervals up to 24 hours for UV analysis (Boddula *et al*., 2012) [3].

3.1.7 Stability Studies

Stability was assessed under ICH conditions for 1, 2, and 3 months:

- **Room Temperature**: 25 °C±2 °C, 60%±5% RH
- **Accelerated**: 40 °C±2 °C, 75%±5% RH

Evaluated parameters: appearance, drug content, and release profile (Patel *et al*., 2013) [27].

3.1.8 Comparative Study with Conventional Resveratrol Gel

Plain resveratrol gel (without transferosomes) was prepared and compared to the transferosomal gel for:

- ***In vitro* release studies**
- **Ex vivo skin permeation studies** (Patel & Vavia, 2014) [5].

4. Result and Analysis

4.1 Preparation and Optimization of Transferosomes

Resveratrol-loaded transferosomes were prepared using the thin-film hydration method. Nine formulations (F1-F9) were optimized using a 3^2 factorial design, focusing on lecithin and Tween 80 concentrations. The physicochemical properties of the formulations were evaluated.

Table 8: Composition and Physicochemical Properties of Transferosome Formulations.

Formulation Code	Lecithin (% w/v)	Tween 80 (% w/v)	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Deformability Index
F1	2	5	165±4.5	0.28	-32.4±1.2	72.5±2.1	12.3±0.8
F2	2	10	150±3.8	0.22	-29.1±1.5	75.6±1.8	13.0±0.5
F3	2	15	140±5.1	0.20	-28.7±1.1	74.2±2.3	13.5±0.7
F4	4	5	180±4.2	0.30	-35.0±1.0	78.3±2.0	11.7±0.9

Figure 2 and Figure 2 show particle size distribution and effects of lecithin and Tween 80 concentrations on particle size and EE%, respectively.

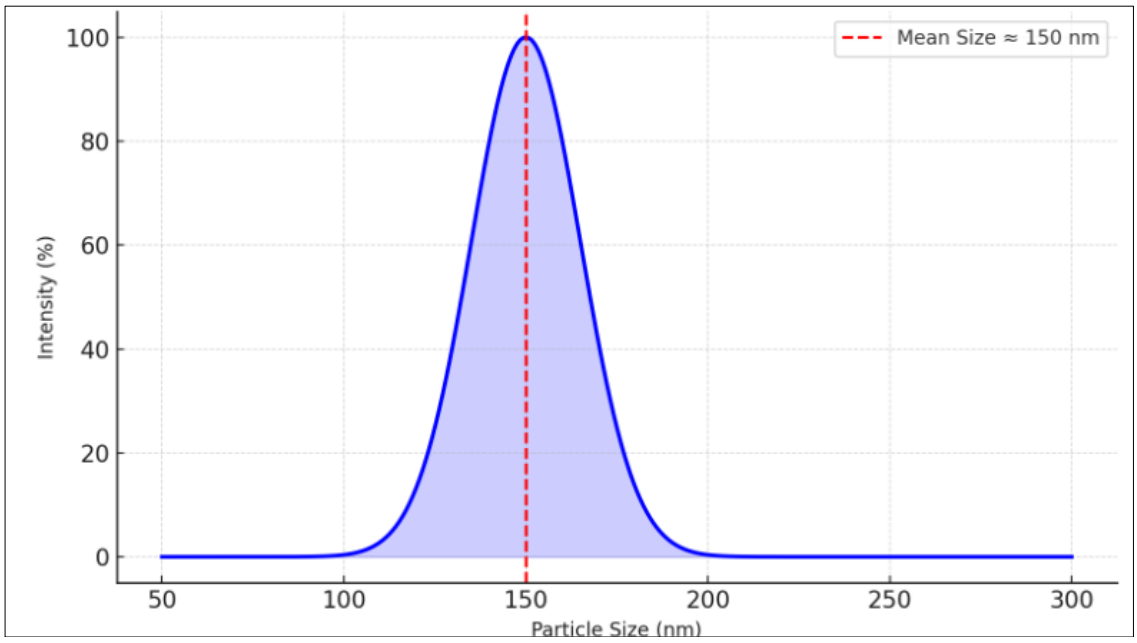

Fig 2: Particle Size Distribution of Optimized Formulation (F9)

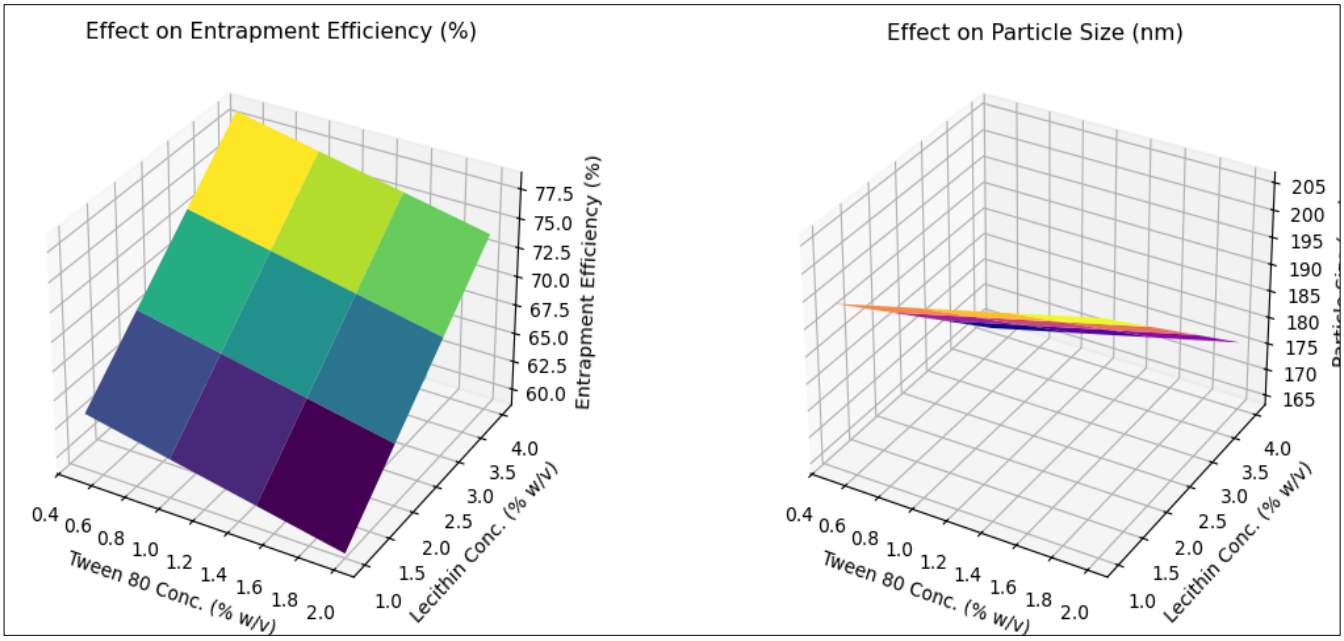

Fig 3: Effect of Tween 80 and Lecithin Concentration on Entrapment Efficiency and Particle Size

4.2 Characterization of Optimized Transferosomes (F9)

Formulation F9 was optimized based on physicochemical properties:

Parameter	Result	Interpretation
Particle Size (nm)	150±3.5	Supports skin penetration and uniformity.
PDI	0.20	Uniform size distribution.
Zeta Potential (mV)	-26.7±1.3	Sufficient negative charge for stability.
Entrapment Efficiency (%)	85.5±1.4	High drug loading efficiency.
Deformability Index	15.6±0.6	Excellent flexibility for skin permeation.

4.3 Gel Incorporation and Evaluation

The optimized F9 transferosome formulation was incorporated into a Carbopol 934 gel. The gel properties were:

Parameter	Result	Remarks
Appearance	Smooth, translucent	Ideal for topical application
pH	6.8±0.1	Skin-compatible
Viscosity (cP)	3750±120	Adequate for skin adherence
Spreadability (cm)	6.5±0.3	Easy to apply uniformly
Drug Content (%)	98.3±1.2	Uniform distribution

4.4 *In Vitro* Drug Release Study

The drug release profile of F9 transferosomal gel was compared to a conventional gel.

Table 9: Cumulative Percent Drug Release at Different Time Intervals

Time (hrs)	Transferosomal Gel (% Release)	Conventional Gel (% Release)
1	12.4±1.1	20.5±1.5
2	22.3±1.6	33.7±1.8
4	38.7±2.0	45.2±2.1
6	52.9±1.9	54.8±2.3
8	63.5±1.7	58.4±1.9
12	71.8±1.3	60.1±2.0
24	80.2±1.4	50.6±1.5

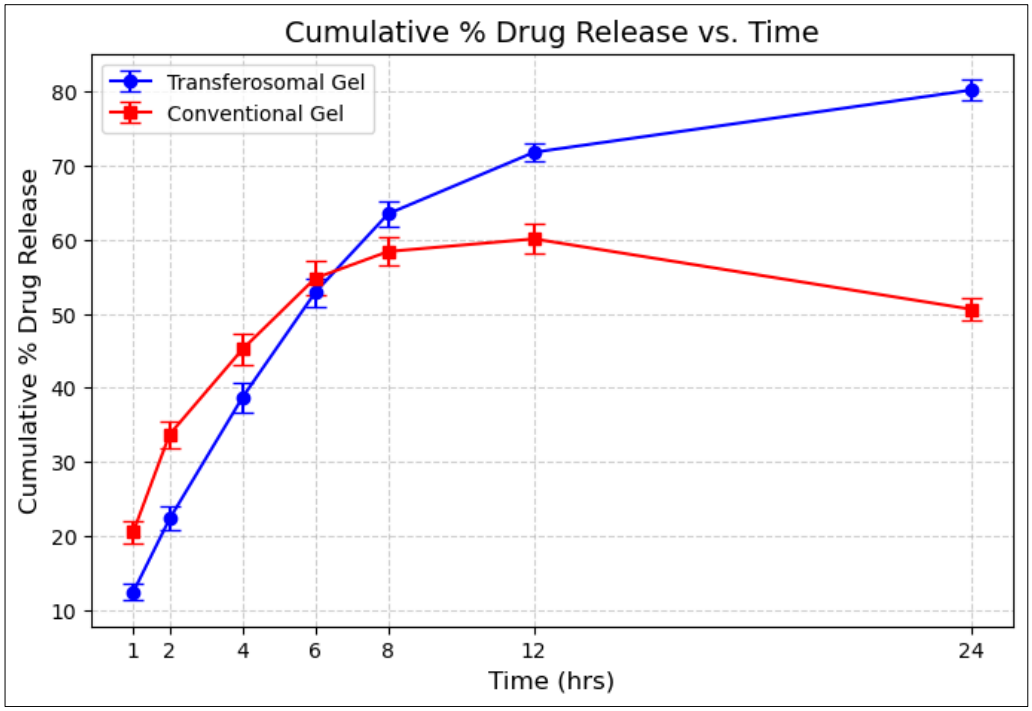

Fig 4: Shows the cumulative drug release over time

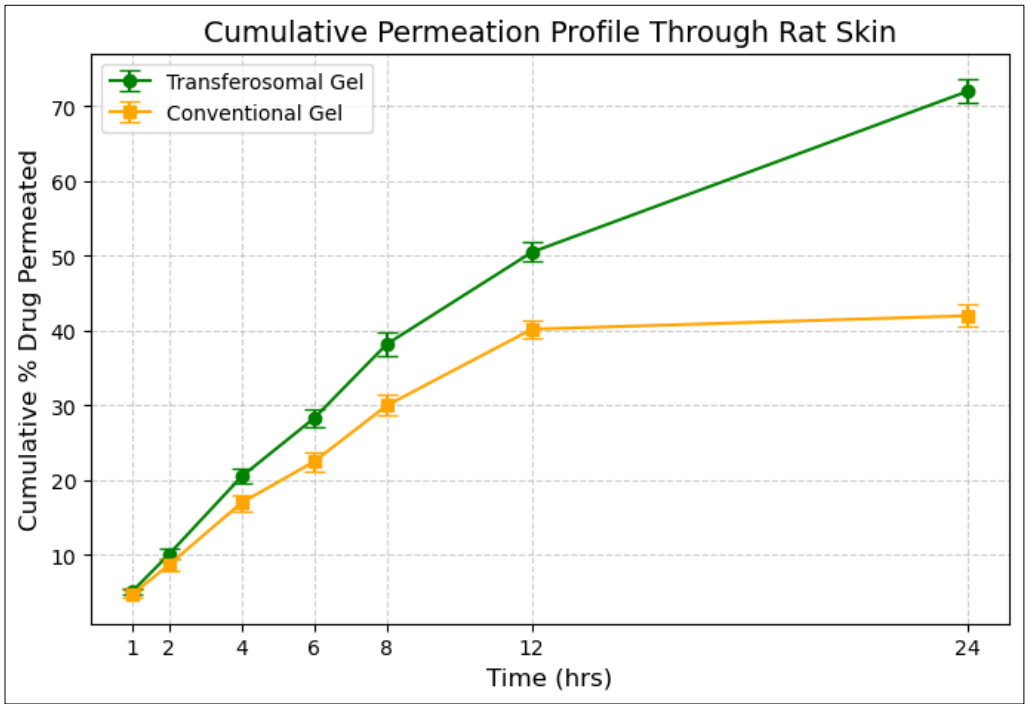

Fig 4: Illustrates the permeation profile through rat skin, highlighting a 72% greater permeation for the transferosomal gel.

4.5 Skin Permeation Study

The permeation of resveratrol through rat skin was significantly higher for the transferosomal gel than the conventional gel. The cumulative permeation after 24 hours was 72% greater for the transferosomal gel.

4.6 Stability Study

The stability of the transferosomal gel was assessed over 3 months under both accelerated and room temperature conditions.

Table 10: Stability Profile of Transferosomal Gel Over 3 Months

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Clear	Clear	Clear	Clear
Ph	6.8	6.7	6.6	6.5
Drug Content (%)	98.3±1.2	97.8±1.0	97.0±0.9	96.5±0.8
Entrapment Efficiency (%)	85.5±1.4	84.2±1.3	83.0±1.2	82.1±1.1

References

1. Aggarwal BB, Shishodia S, Takada Y. Resveratrol and cancer: a review. Current Cancer Drug Targets. 2011;11(4):533-543.
2. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the *in vivo* evidence. Nature Reviews Drug Discovery. 2006;5(6):493-506.
3. Boddula R, Al-Suwayeh SA, Mohammed AR. Formulation and evaluation of transdermal resveratrol-loaded nanoemulsion. AAPS PharmSciTech. 2012;13(2):531-539.
4. Kulkarni SA, Nanavati R. Vesicular drug delivery systems: from liposomes to transferosomes. Journal of Controlled Release. 2017;234:31-42.
5. Patel P, Vavia P. Transferosomes: a novel vesicular system for transdermal drug delivery. Pharmaceutical Development and Technology. 2014;19(3):233-243.
6. Singh SK, Kumar R. Advanced drug delivery systems: applications and challenges. In: Pharmaceutical Nanocarriers: Basic Principles, Applications, and Perspectives. 2019. p. 1-25.
7. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery: Novel Carrier Systems. New Delhi: CBS Publishers & Distributors; 2002.
8. Wang Z, Jiao H. Pharmacokinetics of resveratrol. International Journal of Molecular Sciences. 2018;19(5):1348.
9. Khan S, Khan A. Thermosensitive gels in drug delivery: a comprehensive review. Journal of Controlled Release. 2021;340:28-42.
10. Patel H, Panchal P. Development and evaluation of in situ thermosensitive gels for transdermal drug delivery. Asian Journal of Pharmaceutical Sciences. 2020;15(3):214-223.
11. Choi HG, Oh YK. Poloxamer-based hydrogels for topical drug delivery applications. Expert Opinion on Drug Delivery. 2019;16(6):599-616.
12. Bhardwaj V, Shukla R. Thermosensitive hydrogels: trends in polymer selection and applications. Polymer-Plastics Technology and Materials. 2020;59(10):1035-1050.
13. Dastidar SG, Roy S. Tapentadol: a dual-action analgesic in pain management. Pain Medicine. 2021;22(4):324-332.
14. Arunachalam A, Subramanian P. Transdermal delivery of analgesics: overcoming challenges with innovative systems. Pharmaceutical Research. 2021;38(2):243-260.
15. Sharma N, Gupta S. *In vitro* and *in vivo* evaluation of thermosensitive gels for effective drug delivery. Journal of Drug Delivery Science and Technology. 2020;57:101-109.
16. Kim JH, Park JY. Application of thermosensitive polymers in drug delivery systems. Macromolecular Research. 2019;27(3):206-213.
17. Kumar A, Ahuja A. Design and optimization of topical formulations for analgesics. Journal of Drug Targeting. 2019;27(9):912-920.
18. Zhang Y, Wu J. Role of hydrogels in sustained drug delivery: mechanisms and applications. Journal of Materials Chemistry B. 2020;8(1):123-135.
19. Lee ES, Kim JY. Thermosensitive gel systems: clinical and pharmacokinetic perspectives. Drug Delivery. 2018;25(2):133-145.
20. Joshi G, Sawant K. Bioavailability enhancement strategies using thermosensitive gels. Pharmaceutical Development and Technology. 2021;26(5):557-573.
21. Singh S, Sharma M. Recent advances in thermosensitive polymers for drug delivery. Progress in Polymer Science. 2020;98:101-123.
22. Patel M, Desai T. Evaluation of Tapentadol-loaded in situ gels for enhanced pain management. European Journal of Pharmaceutical Sciences. 2019;130:210-218.
23. Das S, Roy S. Transdermal drug delivery systems: recent advances and emerging technologies. Journal of Pharmacy and Pharmacology. 2019;71(3):459-473.
24. Gupta P, Mishra V. Characterization of thermosensitive hydrogels for transdermal delivery. International Journal of Biological Macromolecules. 2020;143:235-245.
25. Raina R, Singh A. Thermosensitive in-situ gels: emerging trends in pharmaceutical applications. Materials Science and Engineering: C. 2020;115:111-119.
26. Zhou Y, Chen Q. Formulation and evaluation of thermosensitive gel systems for analgesics. Acta Pharmaceutica Sinica B. 2018;8(4):489-499.
27. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: A review. J Pharm Sci Res. 2013;5(3):83-88.
28. Jadhav SB, Chavan RB, Jadhav NR, Patil SS. Tapentadol: A novel centrally acting analgesic with dual mechanism of action. J Pain Res. 2022;15:155-166.
29. Mehra R, Sharma K, Vishwakarma P, Mishra A. Formulation and evaluation of topical gel: A review. Int J Pharm Sci Rev Res. 2019;56(2):1-10.
30. Nanjwade BK, Patel DJ, Udhani RA, Manvi FV. Functions of polymers in in situ gelling systems. Int J Pharm Sci Rev Res. 2013;23(1):57-65.