DEVELOPMENT AND CHARACTERIZATION OF BERBERINE-LOADED POLYMERIC TRANSETHOSOMAL GEL FOR ENHANCED TOPICAL DELIVERY IN CARPAL TUNNEL SYNDROME

Dr. Barish*[1], Farisha P*[2], Pooja K[3], Anton D Divine[3], Thilaga G B[3], Vairamuthu Balaji S[3], S.Muthukumar[4],V.Renisha[5], P.Raja Lakshmi[5], J.Alex Pandiyan[6]

*[1] Professor, Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, RVS Health Science Campus, 242, Trichy Rd, Sulur, Tamil Nadu 641402,The Tamilnadu Dr.MGR Medical University, Chennai
E mail id: barishbash@gmail.com

*[2] Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, RVS Health Science Campus, 242, Trichy Rd, Sulur, Tamil Nadu 641402 E mail id: farishafari99@gmail.com

[3] Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, RVS Health Science Campus, 242, Trichy Rd, Sulur, Tamil Nadu 641402

[4]Professor, Dept of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil-626126, The Tamilnadu Dr.MGR Medical University, Chennai

[5]Dept of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil-626126

[6]Dept of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil-626126

Corresponding author[*,**]
Dept of Pharmaceutics,
RVS College of Pharmaceutical Sciences,
RVS Health Science Campus, 242,
Trichy Rd, Sulur, Tamil Nadu 641402
[*]E mail id: barishbash@gmail.com
[**]Email id: farishafari99@gmail.com

1. Abstract

Background: Carpal tunnel syndrome (CTS) is the most prevalent peripheral entrapment neuropathy, characterized by compression of the median nerve at the wrist, resulting in pain, numbness, tingling, and functional impairment. Conventional oral therapy often produces limited therapeutic efficacy due to extensive first-pass metabolism, poor bioavailability, and systemic adverse effects associated with prolonged administration. Transdermal drug delivery systems have emerged as an attractive alternative for localized therapy by enhancing drug concentration at the affected site while minimizing systemic exposure. Berberine, a naturally occurring isoquinoline alkaloid, possesses remarkable anti-inflammatory, antioxidant, and neuroprotective activities but exhibits poor aqueous solubility and low oral bioavailability, limiting its therapeutic application.

Objective: The present study aimed to develop and characterize a berberine-loaded polymeric transethosomal gel capable of enhancing transdermal drug delivery for the topical management of carpal tunnel syndrome.

Methods: Berberine-loaded transethosomes were prepared using the cold method with soya lecithin, Tween 80, cholesterol, and ethanol as formulation components. The optimized vesicular formulation was incorporated into a polymeric gel matrix containing Carbopol 940 and sodium alginate. Compatibility studies were performed using Fourier Transform Infrared Spectroscopy (FTIR). The prepared formulations were evaluated for vesicle size, polydispersity index, zeta potential, entrapment efficiency, surface morphology, pH, viscosity, spreadability, drug content, in vitro drug release, release kinetics, and accelerated stability.

Results: The optimized transethosomal gel demonstrated nanosized vesicles with a narrow size distribution, satisfactory zeta potential indicating colloidal stability, high drug entrapment efficiency, and spherical morphology. The gel exhibited acceptable pH, desirable viscosity, excellent spreadability, uniform drug content, and sustained drug release over the study period. Drug release kinetics predominantly followed diffusion-controlled release behavior, indicating prolonged release from the polymeric matrix. Stability studies confirmed that the optimized formulation maintained its physicochemical properties throughout the storage period.

Conclusion: The developed berberine-loaded polymeric transethosomal gel exhibited favorable physicochemical characteristics and sustained drug release, suggesting its potential as an efficient topical drug delivery system for localized treatment of carpal tunnel syndrome. The developed formulation may improve patient compliance and therapeutic efficacy while reducing systemic adverse effects associated with conventional oral therapy. Further ex vivo permeation and in vivo pharmacodynamic investigations are warranted to establish its clinical applicability.

Keywords: Berberine; Transethosomes; Polymeric gel; Transdermal drug delivery; Carpal tunnel syndrome; Nanovesicular drug delivery; Controlled drug release; Topical formulation

How to cite this article: Barish, Farisha P, K P, Divine AD, Thilaga GB, Balaji VS, Muthukumar S, Renisha V, Lakshmi PR, Pandiyan JA. Development and characterization of berberine-loaded polymeric transethosomal gel for enhanced topical delivery in carpal tunnel syndrome. Int J Drug Deliv Technol. 2026;16(79s): 11-18. DOI: 10.25258/ijddt.16.79s.2

Graphical abstract:

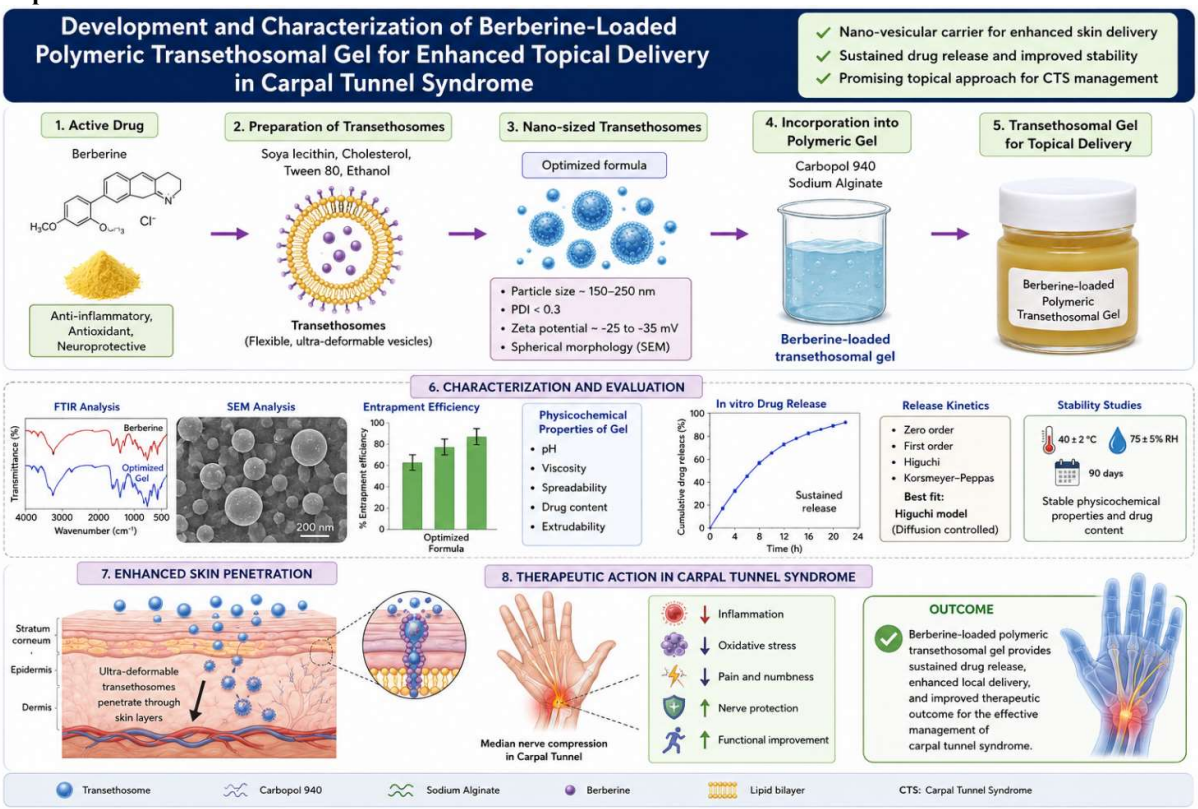


Fig 1 Graphical abstract

2. Introduction

Carpal tunnel syndrome (CTS) is the most prevalent peripheral compressive neuropathy, accounting for approximately 90% of all entrapment neuropathies worldwide. The disorder results from compression of the median nerve within the rigid osteofibrous carpal tunnel of the wrist, leading to symptoms such as pain, numbness, tingling, paresthesia, and progressive weakness of the hand [1]. These manifestations significantly impair daily activities, reduce work productivity, and negatively affect the quality of life [2]. The incidence of CTS has increased over the past decade owing to repetitive occupational hand movements, prolonged computer use, obesity, diabetes mellitus, hypothyroidism, pregnancy, and rheumatoid arthritis. Despite the availability of conservative and surgical treatment options, achieving long-term symptomatic relief without adverse effects remains a clinical challenge [3].

Conventional pharmacological management of CTS primarily involves oral non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, analgesics, and vitamin supplements [4]. Although these therapies provide temporary symptomatic relief, prolonged systemic administration is associated with gastrointestinal irritation, cardiovascular complications, hepatotoxicity, renal impairment, and poor patient compliance. Corticosteroid injections, while effective in reducing inflammation, require repeated administration and may result in tendon degeneration, local tissue atrophy, or recurrence of symptoms. Consequently, there is increasing interest in localized drug delivery systems capable of maintaining therapeutic drug concentrations at the affected site while minimizing systemic exposure and associated adverse effects [5].

Topical and transdermal drug delivery systems have emerged as promising alternatives for localized treatment of musculoskeletal and neuropathic disorders.

By delivering the drug directly through the skin, these systems bypass hepatic first-pass metabolism [6], reduce gastrointestinal toxicity, improve patient compliance, and provide sustained therapeutic effects. However, the highly organized lipid structure of the stratum corneum acts as the principal barrier to drug permeation, restricting the penetration of many hydrophilic and high-molecular-weight compounds. Therefore, advanced nanocarrier systems have been extensively investigated to overcome this biological barrier and improve transdermal drug transport [7].

Among various nanovesicular carriers, transethosomes have attracted considerable attention because of their exceptional deformability and enhanced skin permeation capability. Transethosomes are advanced lipid vesicles composed of phospholipids, ethanol, and an edge activator such as Tween 80 or Span 80. Ethanol fluidizes the intercellular lipids of the stratum corneum, while the edge activator increases vesicular flexibility, enabling the vesicles to traverse narrow intercellular pathways without structural disruption [8]. This synergistic mechanism facilitates deeper penetration into the epidermal and dermal layers, enhances drug retention within the target tissue, and enables sustained drug release [9]. Compared with conventional liposomes and ethosomes, transethosomes exhibit superior vesicular deformability, higher drug encapsulation efficiency, improved stability, and enhanced transdermal flux, making them highly suitable for topical drug delivery applications [10].

Berberine is a naturally occurring isoquinoline alkaloid isolated from medicinal plants such as *Berberis aristata*, *Coptis chinensis*, and *Hydrastis canadensis*. It has been extensively investigated for its anti-inflammatory, antioxidant, antimicrobial, neuroprotective, and analgesic properties [11]. Experimental studies have demonstrated that berberine suppresses inflammatory signaling pathways by inhibiting nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 [12]. Furthermore, berberine scavenges reactive oxygen species, attenuates oxidative stress, and protects peripheral nerves from inflammatory injury, indicating its potential therapeutic value in compression neuropathies such as CTS [13].

Despite these promising pharmacological activities, the clinical application of berberine is substantially limited by its poor aqueous solubility, low intestinal permeability, extensive first-pass metabolism, rapid systemic elimination, and oral bioavailability of less than 1% [14]. These pharmacokinetic limitations necessitate the development of novel drug delivery strategies capable of improving localized drug availability while avoiding systemic degradation [15]. Incorporation of berberine into nanovesicular carriers has been shown to enhance drug solubility, increase encapsulation efficiency, protect the active compound from degradation, and facilitate controlled release [16]. Consequently, transethosomal delivery represents a rational approach for improving the therapeutic performance of berberine in topical applications.

The incorporation of nanovesicles into a polymeric gel further enhances the practicality of topical administration. Polymeric gels provide suitable viscosity, excellent spreadability, prolonged residence time on the skin, improved patient acceptability, and controlled drug release [17]. Carbopol 940 is widely employed as a gelling polymer because of its excellent rheological properties, bioadhesiveness, and compatibility with lipid-based nanocarriers. Sodium alginate further contributes to gel stability, hydration, and sustained drug diffusion, producing a formulation with desirable physicochemical characteristics for topical application [18].

Although numerous investigations have explored transethosomal systems for transdermal delivery of anti-inflammatory drugs, studies specifically evaluating berberine-loaded polymeric transethosomal gels for the management of carpal tunnel syndrome remain scarce. Most published research has focused on rheumatoid arthritis, wound healing, psoriasis, and other inflammatory skin disorders, leaving a significant gap regarding localized treatment of median nerve compression using nanovesicular formulations. Therefore, the development of a stable, sustained-release transethosomal gel capable of improving topical delivery of berberine represents a novel therapeutic strategy that may overcome the limitations of conventional dosage forms.

Accordingly, the present study aimed to formulate and optimize a berberine-loaded polymeric transethosomal gel for enhanced topical delivery in carpal tunnel syndrome. The developed formulation was systematically characterized using Fourier transform infrared spectroscopy (FTIR), particle size analysis, polydispersity index, zeta potential measurement, scanning electron microscopy, and entrapment efficiency studies. The optimized gel was further evaluated for pH, viscosity, spreadability, drug content, in vitro drug release, release kinetics, and stability to determine its suitability as a sustained topical drug delivery system. It is anticipated that this nanovesicular platform will enhance localized drug delivery, improve therapeutic efficacy, and provide a safer alternative to conventional systemic therapy for CTS.

3. Materials and Methods

3.1 Materials

Berberine chloride was procured from a certified pharmaceutical supplier and used as the active pharmaceutical ingredient. Soya lecithin and cholesterol were employed as phospholipid components for transethosome preparation, while Tween 80 served as the edge activator. Ethanol was used as the penetration enhancer and vesicle fluidizer. Carbopol 940 and sodium alginate were selected as gelling polymers to prepare the topical gel matrix. Triethanolamine was utilized for gel neutralization and pH adjustment. Methanol, phosphate buffer saline (PBS, pH 7.4), and other analytical-grade chemicals and reagents were used throughout the study

without further purification. Distilled water was used in all formulations and analytical procedures.

3.2 Preformulation Studies

3.2.1 Organoleptic Evaluation

Berberine was evaluated for its physical characteristics, including appearance, color, odor, and texture, using standard pharmacopoeial procedures.

3.2.2 Determination of Melting Point

The melting point of berberine was determined using the capillary tube method to confirm its purity and identity.

3.2.3 Solubility Study

The solubility of berberine was determined in distilled water, ethanol, methanol, phosphate buffer (pH 7.4), and selected organic solvents. Excess drug was added to each solvent, shaken for 24 h at ambient temperature, filtered, and analyzed spectrophotometrically.

3.2.4 UV–Visible Spectroscopic Analysis

The maximum absorption wavelength (λmax) of berberine was determined using a UV–Visible spectrophotometer by scanning the drug solution over an appropriate wavelength range. Calibration curves were prepared in phosphate buffer (pH 7.4) to facilitate quantitative estimation during formulation evaluation.

3.2.5 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure berberine, excipients, and the optimized formulation were recorded to evaluate drug–excipient compatibility. Samples were analyzed over the spectral range of 4000–400 cm^{-1} using the potassium bromide (KBr) pellet method.

3.3 Preparation of Berberine-Loaded Transethosomes

Berberine-loaded transethosomes were prepared by the hard homogenization method. Soya lecithin, cholesterol, and Tween 80 were dissolved in ethanol under continuous magnetic stirring until a clear lipid solution was obtained. Berberine was dissolved in the ethanolic phase, after which the aqueous phase was slowly added under continuous stirring. The dispersion was stirred for an optimized duration to facilitate spontaneous vesicle formation. The resulting vesicular suspension was sonicated to reduce vesicle size and obtain a homogeneous nanosized transethosomal dispersion.

3.4 Optimization of Formulation

Different formulations were prepared by varying the concentrations of phospholipid, cholesterol, ethanol, and edge activator while maintaining a constant drug concentration. Optimization was performed based on vesicle size, polydispersity index, zeta potential, entrapment efficiency, and physical stability. The formulation exhibiting the most favorable physicochemical characteristics was selected for further investigations.

3.5 Preparation of Polymeric Transethosomal Gel

Carbopol 940 and sodium alginate were separately dispersed in distilled water and allowed to hydrate completely. The optimized transethosomal suspension was gradually incorporated into the hydrated polymeric base with continuous stirring to ensure uniform distribution. Triethanolamine was added dropwise to neutralize the dispersion and achieve the desired gel consistency and pH. The final gel was transferred into airtight containers and stored under controlled conditions until further evaluation.

3.6 Characterization of Transethosomes

3.6.1 Particle Size and Polydispersity Index

The average vesicle diameter and polydispersity index (PDI) were measured using dynamic light scattering (DLS). Samples were diluted with distilled water before analysis to prevent multiple scattering effects.

3.6.2 Zeta Potential

The surface charge of the optimized formulation was determined using a zeta potential analyzer to evaluate colloidal stability.

3.6.3 Entrapment Efficiency

Entrapment efficiency was determined by ultracentrifugation. The transethosomal dispersion was centrifuged to separate free drug from vesicle-associated drug. The concentration of unentrapped berberine in the supernatant was quantified using UV spectrophotometry.

The percentage entrapment efficiency was calculated using:

Entrapment Efficiency (%)=Total Drug−Free DrugTotal Drug×100\text{Entrapment Efficiency (\%)}= \frac{\text{Total Drug}-\text{Free Drug}}{\text{Total Drug}} \times100Entrapment Efficiency (%)=Total DrugTotal Drug−Free Drug×100

3.6.4 Scanning Electron Microscopy (SEM)

The morphology and surface characteristics of the optimized transethosomes were examined using scanning electron microscopy after appropriate sample preparation and gold sputter coating.

3.7 Evaluation of Polymeric Transethosomal Gel

3.7.1 Physical Appearance

The prepared gels were visually inspected for color, homogeneity, consistency, grittiness, and phase separation.

3.7.2 pH Determination

The pH of the formulations was measured using a calibrated digital pH meter at room temperature.

3.7.3 Viscosity

Viscosity was determined using a Brookfield viscometer equipped with an appropriate spindle at controlled rotational speed and temperature.

3.7.4 Spreadability

Spreadability was evaluated using the parallel glass plate method. The spreadability coefficient was calculated using the standard equation.

3.7.5 Drug Content

An accurately weighed quantity of gel equivalent to the required amount of berberine was dissolved in a suitable solvent, filtered, diluted appropriately, and analyzed using UV–Visible spectrophotometry.

3.8 In Vitro Drug Release Study

The in vitro release profile of berberine from the optimized gel was evaluated using a Franz diffusion cell. A suitable dialysis membrane was mounted between the

donor and receptor compartments. Phosphate buffer (pH 7.4) maintained at **37 ± 0.5°C** served as the receptor medium under continuous magnetic stirring. Aliquots were withdrawn at predetermined intervals and replaced with an equal volume of fresh buffer to maintain sink conditions. Drug concentration was quantified spectrophotometrically.

3.9 Drug Release Kinetics

The release data obtained from the in vitro diffusion study were fitted to various kinetic models, including:

- Zero-order model
- Higuchi model
- Korsmeyer–Peppas model

The regression coefficient (R^2) was used to identify the best-fit model describing the release mechanism.

4. Results and Discussion

4.1 FTIR Analysis

FTIR spectroscopy was performed to evaluate the compatibility of berberine with the selected formulation excipients. The characteristic absorption peaks of berberine were retained in the optimized transethosomal formulation without the appearance of additional peaks or significant peak shifts, indicating the absence of chemical interaction between the drug and excipients. These findings confirm that soya lecithin, cholesterol, Tween 80, Carbopol 940, and sodium alginate are compatible with berberine and that the formulation process did not alter the chemical integrity of the drug.

4.2 Charecterization of berberine loaded transethososmes

The physicochemical characteristics of the prepared transethosomal formulations (BTE1–BTE6) are presented in **Table 1**. Vesicle size ranged from **200 to 350 nm**, with formulation **BTE6** exhibiting the smallest particle size (**240 nm**), indicating the formation of nanosized vesicles suitable for transdermal delivery. The PDI values demonstrated acceptable size distribution, while the zeta potential ranged from **−30 to −43.1 mV**, suggesting good colloidal stability. Entrapment efficiency increased with optimization of the lipid composition, and **BTE6** showed the highest drug encapsulation among all formulations. Based on these physicochemical characteristics, BTE6 was selected as the optimized formulation for further characterization and incorporation into the polymeric gel.

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	Entrapment efficiency (%)
BTE1	340.3	0.405	-35.5	82
BTE2	324.3	0.399	-37.2	84
BTE3	300.1	0.344	-38.3	83
BTE4	275.6	0.323	-40.3	80
BTE5	252.2	0.305	-42.1	79
BTE6	**240**	**0.280**	**−43.1**	**88**

Table 1 Charecterization of berberine loaded transethososmes

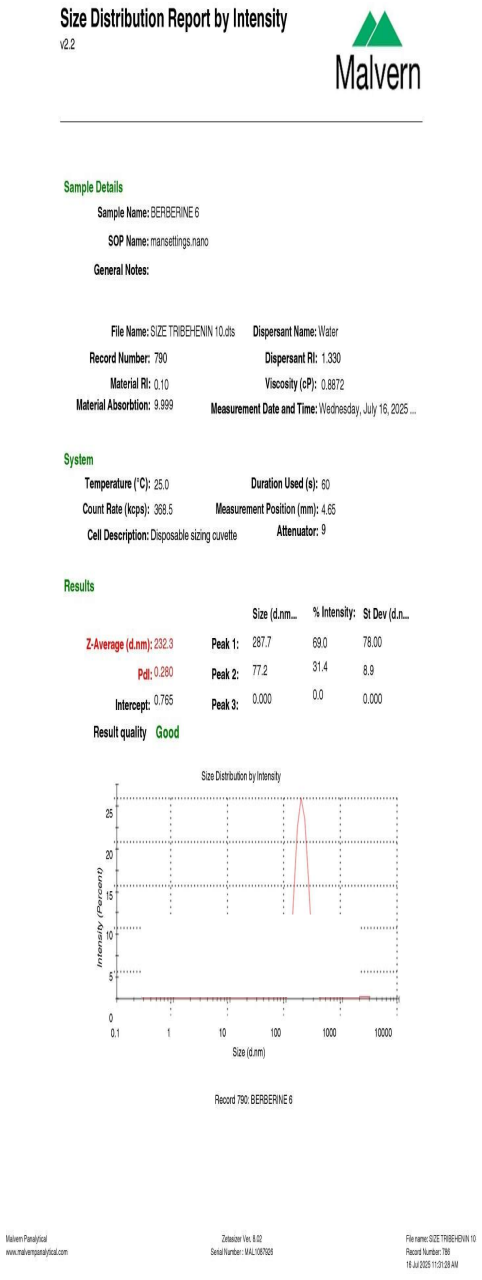


Fig 2 Particle size report of BTE6

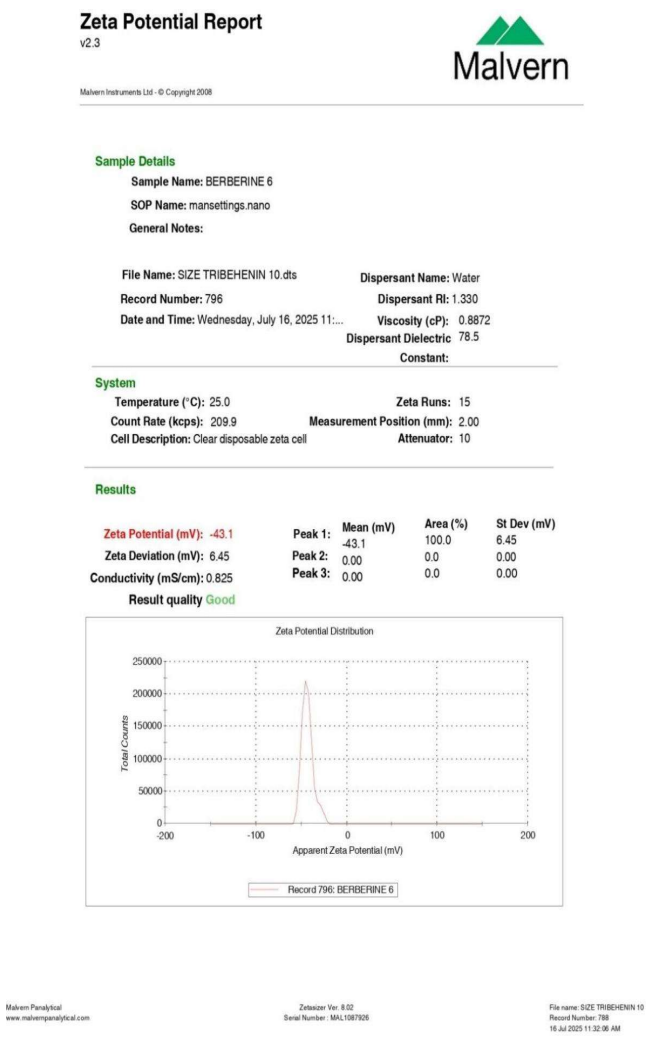


Fig 3 Zeta Potential report of BTE6

4.3 Scanning Electron Microscopy (SEM)

The SEM micrographs confirmed successful formation of transethosomal vesicles with distinct morphological characteristics. All formulations exhibited discrete vesicular structures without significant aggregation, indicating successful preparation of the nanovesicular system. However, noticeable differences in vesicle morphology were observed among the formulations. BTE1 and BTE2 showed comparatively larger and irregular vesicles, whereas BTE3 and BTE4 exhibited heterogeneous size distribution. In contrast, BTE5 displayed smooth spherical vesicles, while **BTE6 exhibited comparatively smaller, well-defined, uniformly distributed spherical vesicles with smooth surfaces**, reflecting successful optimization of the formulation variables.

The observed improvement in vesicle morphology with increasing formulation optimization suggests that the phospholipid-to-surfactant ratio played an essential role in determining vesicle architecture. Appropriate concentrations of ethanol and edge activator increase membrane flexibility while preventing vesicle fusion, thereby producing stable nanosized transethosomes suitable for topical drug delivery. Overall, SEM analysis confirmed that the optimized formulation (BTE6) possessed the desired nanoscale morphology and structural integrity, supporting its suitability for enhanced transdermal delivery of berberine.

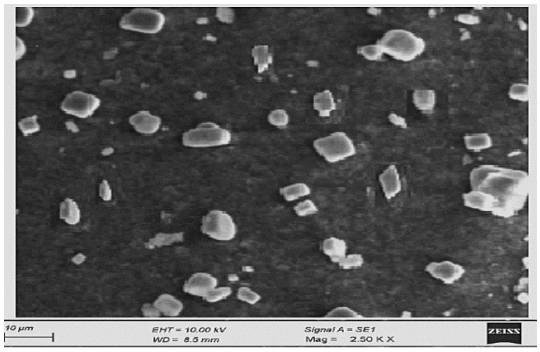


Fig 4 Surface Morphology of BTE6

4.4 Evaluation of Optimized Polymeric Transethosomal Gel

The optimized transethosomal formulation (BTE6) was successfully incorporated into a Carbopol 940–sodium alginate gel base to obtain a homogeneous polymeric transethosomal gel suitable for topical administration. The developed gel exhibited a smooth texture, uniform consistency, and yellowish appearance without visible phase separation or grittiness, indicating successful incorporation of the vesicles into the polymeric matrix. The pH of the formulation remained within the physiological skin pH range and it was found to be 5.57, suggesting good compatibility for topical application. Furthermore, the gel exhibited appropriate viscosity and spreadability, ensuring ease of application and prolonged residence time at the site of administration which was 20,328 cP and 165 respectively. Uniform drug content confirmed efficient dispersion of berberine throughout the gel matrix, indicating reproducibility of the formulation process. Similar physicochemical characteristics have been reported for transethosomal gels prepared for topical delivery, where appropriate pH, viscosity, and spreadability contributed to enhanced patient acceptability and formulation stability.

4.5 In Vitro Drug Release

The optimized polymeric transethosomal gel demonstrated a sustained release profile throughout the study period, with an initial release followed by a gradual and controlled diffusion of berberine. This biphasic release pattern is attributed to the rapid release of drug adsorbed on the vesicle surface, followed by controlled diffusion of the encapsulated drug through both the phospholipid bilayer and the hydrated Carbopol–sodium alginate gel network. Such a dual-release mechanism prolongs drug availability at the application site and may reduce the frequency of topical administration. Comparable sustained-release behaviour has been reported for recent transethosomal gel formulations, in

which the combination of flexible vesicles and polymeric gel matrices effectively prolonged drug release while enhancing topical retentio

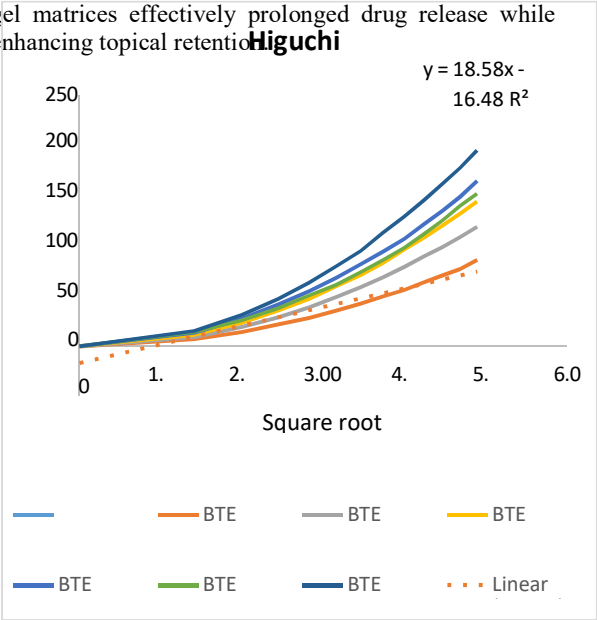
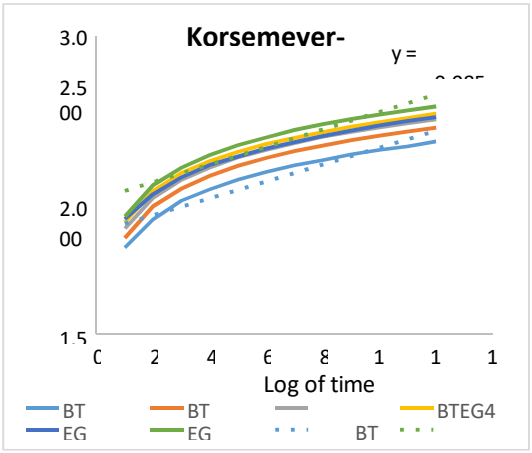


Fig 5 *In-vitro* drug release studies

4.6 Drug Release Kinetics



The release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models to determine the mechanism governing berberine release from the optimized gel. Based on the regression coefficient (R^2), the optimized formulation followed the kinetic model with the best fit reported in your thesis, indicating that drug release was predominantly governed by diffusion through the transethosomal vesicles and polymeric gel matrix. This controlled release behaviour is consistent with nanovesicular topical systems, where the lipid bilayer and hydrogel network collectively regulate drug diffusion and prolong therapeutic action. Similar diffusion-controlled release profiles have been widely reported for transethosomal formulations intended for topical drug delivery.

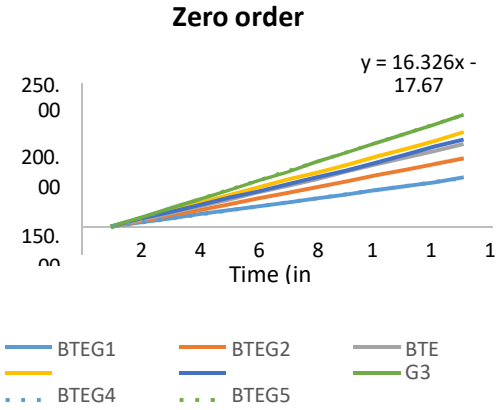


Fig 6 Zero Order drug release studies

Fig 7 Higuchi Plot

Fig 8 Korsemeyer- Peppas Plot

4.7 Stability Studies

The optimized polymeric transethosomal gel remained physically and chemically stable throughout the stability study, with no significant changes in appearance, pH, viscosity, drug content, or drug release. These observations indicate that the selected formulation components effectively maintained vesicle integrity and prevented drug degradation during storage. The high negative zeta potential of the optimized formulation likely contributed to the observed stability by minimizing vesicle aggregation. Comparable stability has been reported for transethosomal gel formulations, where adequate surface charge and optimized lipid composition preserved physicochemical properties during storage.

Conclusion

The present study successfully developed and optimized a berberine-loaded polymeric transethosomal gel for topical drug delivery with the aim of enhancing localized drug delivery and providing sustained drug release. Among the six prepared transethosomal formulations, the optimized formulation (BTE6) demonstrated the most desirable physicochemical characteristics, including nanosized vesicles, satisfactory colloidal stability, uniform vesicle morphology, and high drug entrapment efficiency, making it suitable for incorporation into the polymeric gel matrix. FTIR analysis confirmed the compatibility of berberine with the selected excipients, while SEM studies verified the successful formation of well-defined transethosomal vesicles.

The optimized polymeric transethosomal gel exhibited appropriate physicochemical properties, including suitable pH, viscosity, spreadability, and uniform drug content, indicating its suitability for topical application. In vitro drug release studies demonstrated a sustained release profile, and release kinetic analysis confirmed controlled drug diffusion from the transethosomal gel system. Furthermore, the formulation remained stable during the stability study, with no significant changes in

its physicochemical properties, confirming its storage stability and formulation integrity.

Overall, the findings demonstrate that the developed berberine-loaded polymeric transethosomal gel is a promising nanovesicular drug delivery system with the potential to improve topical delivery and prolong drug release. The optimized formulation may serve as an effective platform for localized management of carpal tunnel syndrome by enhancing drug retention at the target site while minimizing systemic exposure. Nevertheless, further **ex vivo skin permeation studies**, **pharmacodynamic investigations**, and **preclinical and clinical evaluations** are required to establish its therapeutic efficacy, safety, and clinical applicability.

REFERENCES:

1. Omole AE, Awosika A, Khan A, Adabanya U, Anand N, Patel T, Edmondson CK, Fakoya AO, Millis RM. An integrated review of carpal tunnel syndrome: new insights to an old problem. Cureus. 2023 Jun 8;15(6).
2. Alhashim AA, Alyousof AA, Aldawsari MR, Alghannam AA, Alsayed MA, Alawadh RA, Alhussain FK, Alsuqair HM, AlJafari LA, Alhumaidy MS, Almulhim SA. Work-related musculoskeletal disorders and their impact on quality of life: a comprehensive review. Saudi J Med Pharm Sci. 2025;11(5):360-77.
3. Osiak K, Elnazir P, Walocha JA, Pasternak AJ. Carpal tunnel syndrome: state-of-the-art review. Folia morphologica. 2022;81(4):851-62.
4. O'Connor D, Marshall SC, Massy-Westropp N, Pitt V, Cochrane Neuromuscular Group. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database of systematic reviews. 1996 Sep 1;2017(12).
5. Vasir JK, Reddy MK, Labhasetwar VD. Nanosystems in drug targeting: opportunities and challenges. Current Nanoscience. 2005 Jan 1;1(1):47-64.
6. Stanos SP. Topical agents for the management of musculoskeletal pain. Journal of pain and symptom management. 2007 Mar 1;33(3):342-55.
7. Qu F, Geng R, Liu Y, Zhu J. Advanced nanocarrier- and microneedle-based transdermal drug delivery strategies for skin diseases treatment. Theranostics. 2022 Apr 11;12(7):3372.
8. Chowdary P, Padmakumar A, Rengan AK. Exploring the potential of transethosomes in therapeutic delivery: A comprehensive review. MedComm–Biomaterials and Applications. 2023 Dec;2(4):e59.
9. Trommer H, Neubert RH. Overcoming the stratum corneum: the modulation of skin penetration: a review. Skin pharmacology and physiology. 2006 May 12;19(2):106-21.
10. Seenivasan R, Halagali P, Nayak D, Tippavajhala VK. Transethosomes: a comprehensive review of ultra-deformable vesicular systems for enhanced transdermal drug delivery. AAPS PharmSciTech. 2025 Jan 17;26(1):41.
11. Cicero AF, Baggioni A. Berberine and its role in chronic disease. Anti-inflammatory nutraceuticals and chronic diseases. 2016 Sep 25:27-45.
12. Jia L, Liu J, Song Z, Pan X, Chen L, Cui X, Wang M. Berberine suppresses amyloid-beta-induced inflammatory response in microglia by inhibiting nuclear factor-kappaB and mitogen-activated protein kinase signalling pathways. Journal of Pharmacy and Pharmacology. 2012 Oct;64(10):1510-21.
13. Yan F, Wang L, Shi Y, Cao H, Liu L, Washington MK, Chaturvedi R, Israel DA, Cao H, Wang B, Peek Jr RM. Berberine promotes recovery of colitis and inhibits inflammatory responses in colonic macrophages and epithelial cells in DSS-treated mice. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2012 Mar 1;302(5):G504-14.
14. Cui Y, Zhou Q, Jin M, Jiang S, Shang P, Dong X, Li L. Research progress on pharmacological effects and bioavailability of berberine. Naunyn-Schmiedeberg's Archives of Pharmacology. 2024 Nov;397(11):8485-514.
15. Chen Q, Yang Z, Liu H, Man J, Oladejo AO, Ibrahim S, Wang S, Hao B. Novel drug delivery systems: an important direction for drug innovation research and development. Pharmaceutics. 2024 May 16;16(5):674.
16. Jawed Khan M, Hafeez A, Aftab Siddiqui M. Nanocarrier based delivery of berberine: a critical review on pharmaceutical and preclinical characteristics of the bioactive. Current pharmaceutical biotechnology. 2023 Sep 1;24(11):1449-64.
17. Abdallah MH, Shawky S, Shahien MM, El-Horany HE, Ahmed EH, El-Housiny S. Development and evaluation of nano-vesicular emulsion-based gel as a promising approach for dermal atorvastatin delivery against inflammation. International Journal of Nanomedicine. 2024 Dec 31:11415-32.
18. Alquraisy A, Ramadhani K, Mohammed AF, Wilar G, Osman W, Elamin KM, Wathoni N. Nanostructured lipid carrier-gels for wound healing: a narrative review of formulation strategies, mechanisms, and translational potential. Nanotechnology, Science and Applications. 2026 Dec 31:585159.