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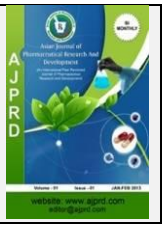

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Research Article

Formulation and In Vitro Evaluation of Levetiracetam Transdermal Patches

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A B S T R A C T

Long-term epilepsy management requires maintaining stable therapeutic plasma concentrations, which is often challenging with orally administered Levetiracetam because of its short dosing interval requirements and extensive hepatic first-pass metabolism. The present investigation aimed to formulate and evaluate a novel matrix-type transdermal drug delivery system (TDDS) employing a synergistic combination of natural Ficus carica fruit mucilage and synthetic polymers, namely HPMC K100 and Eudragit S100, to achieve sustained and controlled drug release. Five formulations (LTP1–LTP5) were prepared using the solvent casting method. The developed transdermal patches were evaluated for various physicochemical parameters, including weight variation, thickness, folding endurance, and drug content uniformity. Compatibility and possible molecular interactions between the drug and polymers were analyzed using FT-IR spectroscopy, while in vitro drug diffusion studies were performed using a Franz diffusion cell over a 24-hour period.FT-IR analysis confirmed the absence of significant drug–polymer interactions, indicating the chemical stability of Levetiracetam within the polymeric matrix. The prepared patches demonstrated satisfactory uniformity, with drug content ranging from 97.5% to 99.4% and thickness values between 138 and 148 µm. Mechanical characterization revealed good flexibility and durability, with folding endurance values reaching up to 172 folds. Among all formulations, LTP4 containing an optimized ratio of natural and synthetic polymers showed the best performance, exhibiting a cumulative drug release of 98.85% over 24 hours, following matrix diffusion-controlled release kinetics.The study concludes that the optimized LTP4 transdermal patch successfully provided sustained release of Levetiracetam and may serve as a promising non-invasive alternative to conventional oral therapy, potentially improving therapeutic efficacy, patient compliance, and long-term epilepsy management.

Keywords: Levetiracetam; *Ficus carica* mucilage; Transdermal Drug Delivery; Hybrid Polymers; Matrix-diffusion; Sustained Release; Epilepsy Management; Solvent Casting

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INTRODUCTION:

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. It affects millions of individuals worldwide and often requires long-term pharmacotherapy for effective control. The primary goal of antiepileptic treatment is to maintain consistent therapeutic drug levels in the systemic circulation while minimizing adverse effects and improving patient adherence. Levetiracetam is a widely prescribed second-generation antiepileptic drug due to its broad spectrum of activity, favorable safety profile, and minimal drug–drug interactions.

Despite these advantages, its conventional oral administration is associated with certain limitations, including the need for frequent dosing and variability in plasma drug concentrations. In addition, first-pass hepatic metabolism and gastrointestinal factors may influence drug bioavailability, potentially affecting therapeutic outcomes.

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to oral dosage forms, offering several advantages such as avoidance of first-pass metabolism, sustained drug release, improved patient compliance, and reduced dosing frequency. Furthermore, transdermal systems provide controlled and continuous drug input, which is particularly beneficial in chronic

conditions like epilepsy where stable plasma levels are essential.

In recent years, there has been growing interest in the use of natural polymers in pharmaceutical formulations due to their biocompatibility, biodegradability, and eco-friendly nature. Ficus carica fruit mucilage is a natural polymer known for its film-forming ability and swelling characteristics, making it suitable for transdermal applications. When combined with synthetic polymers such as Hydroxypropyl Methylcellulose (HPMC K100) and Eudragit S100, it can form a hybrid matrix system capable of modulating drug release effectively.

The present study focuses on the development and evaluation of a matrix-type transdermal patch of Levetiracetam using a synergistic blend of natural and synthetic polymers. The objective was to achieve a controlled and sustained drug release profile over an extended period, thereby enhancing therapeutic efficacy and patient compliance. The prepared formulations were systematically evaluated for their physicochemical properties, drug–polymer compatibility, and in vitro drug release behavior.

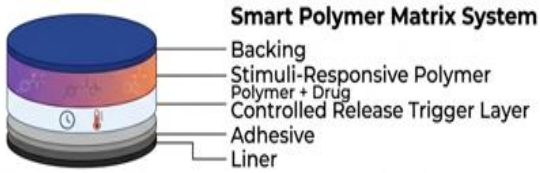

Figure 1: Transdermal Patch

Material and Methods:

Materials

Levetiracetam was obtained as a gift sample from a reputed pharmaceutical source. Ficus carica fruit mucilage was isolated in the laboratory and used as a natural polymer. Hydroxypropyl methylcellulose (HPMC K100) and Eudragit S100 were employed as synthetic polymers for matrix formation. Glycerol was used as a plasticizer, while oleic acid served as a permeation enhancer. Methylparaben and propylparaben were incorporated as preservatives. A mixture of dichloromethane and methanol (1:1) was used as the solvent system. All chemicals and reagents used were of analytical grade.

Preparation of Ficus carica Mucilage

Fresh fruits of Ficus carica were cleaned, peeled, and crushed to obtain the pulp. The pulp was soaked in distilled water and heated gently to facilitate extraction of mucilage. The resulting mixture was filtered through muslin cloth to separate the marc. The filtrate was treated with an appropriate non-solvent to precipitate the mucilage, which was then collected, dried at controlled temperature, and powdered. The dried mucilage was stored in a desiccator until furtehr use.

Formulation of Transdermal Patches

Matrix-type transdermal patches containing Levetiracetam were prepared by the solvent casting method. The compositions of different formulations (LTP1–LTP5) are presented in Table 1.

Accurately weighed quantities of polymers (Ficus carica mucilage, HPMC K100, and Eudragit S100) were dissolved in a dichloromethane:methanol solvent mixture (1:1) under continuous stirring to obtain a uniform polymeric solution. Levetiracetam (100 mg) was then added to the solution and mixed thoroughly to ensure uniform dispersion. Glycerol (80 mg) was incorporated as a plasticizer, followed by the addition of oleic acid (0.75 ml) as a permeation enhancer. Methylparaben (0.5 mg) and propylparaben (0.1 mg) were added to prevent microbial growth. The resulting mixture was stirred until a homogeneous solution was obtained.The final solution was cast onto a clean, leveled glass surface and allowed to dry at room temperature for 24 hours to facilitate solvent evaporation. After drying, the films were carefully peeled off and cut into patches of suitable size. The prepared patches were stored in a desiccator until further evaluation.

Table 1: Composition of Levetiracetam Transdermal Patches (LTP1–LTP5)

INGRIDIENTS	LTP1	LTP2	LTP3	LTP4	LTP5
Drug (mg)	100	100	100	100	100
Ficus carica Mucilage (mg)	400	200	200	100	200
HPMC K100 (mg)	--	200	--	150	100
Eudragit S100 (mg)	--	--	200	150	100
Glycerol (mg)	80	80	80	80	80
Oleic Acid (ml)	0.75	0.75	0.75	0.75	0.75
Methylparaben(mg)	0.5	0.5	0.5	0.5	0.5
Propylparaben (mg)	0.1	0.1	0.1	0.1	0.1
DCM: Methanol (1:1)	15 ml	15 ml	15 ml	15 ml	15 ml

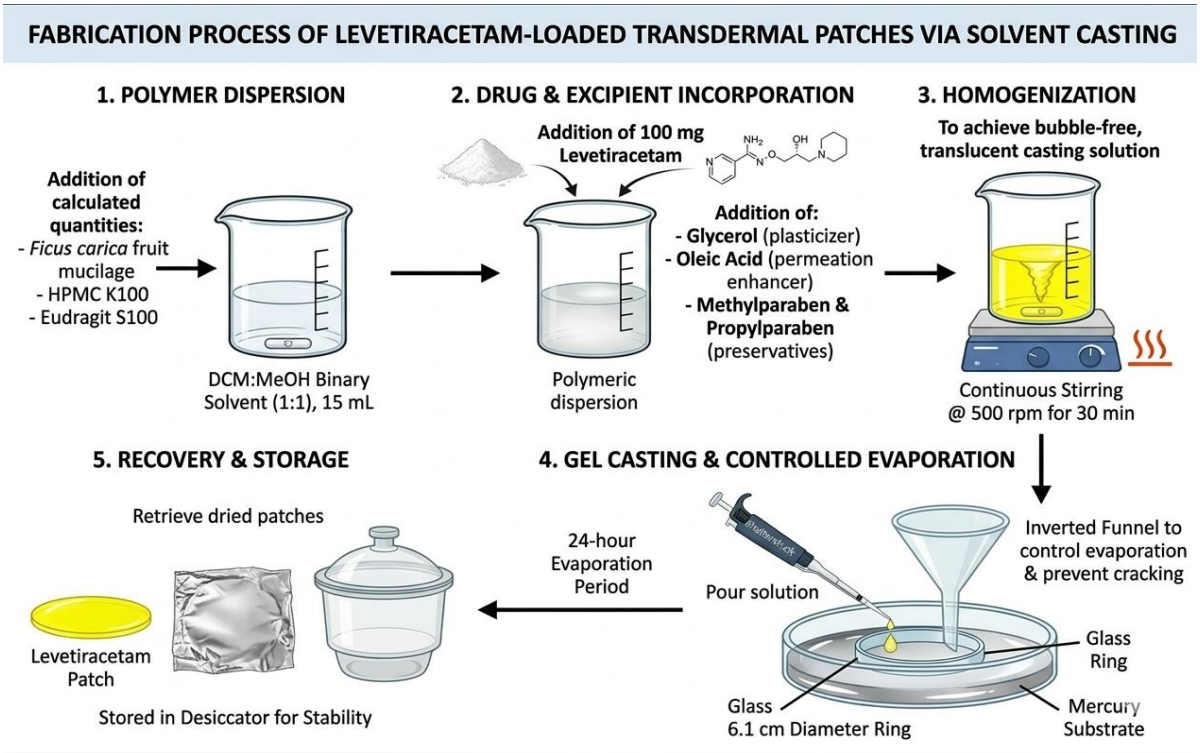

Figure 2: Fabrication process of transdermal patch

EVALUATION OF TRANSDERMAL PATCHES

The prepared transdermal patches were evaluated using standard procedures to determine their physicochemical characteristics, mechanical properties, and drug release behavior.

Physical Appearance

All patches were visually examined for uniformity in color, clarity, smoothness, and flexibility. The films were also checked for the presence of air bubbles, cracks, or any surface irregularities.

Weight Uniformity

Individual patches of identical dimensions were selected randomly and weighed using a calibrated digital balance. The average weight and standard deviation were calculated to assess uniformity among the formulations.

%Weight Variation= Individual weight−Average weight / Average weight ×100

Thickness Measurement

The thickness of each patch was measured at three different positions using a micrometer screw gauge. The mean thickness was calculated to ensure consistency in film casting.

Folding Endurance

Folding endurance was determined by repeatedly folding a patch at the same location until it showed signs of breaking. The number of folds required to cause breakage was recorded as an indicator of mechanical strength and flexibility.

Drug Content Determination

A patch of known area was cut and dissolved in a suitable solvent with continuous stirring to ensure complete extraction of the drug. The solution was filtered, suitably diluted, and analyzed using a UV spectrophotometer at the predetermined wavelength. Drug content was calculated as a percentage of the theoretical value.

%Drug Content= Actual drug content / Theoretical drug content ×100

Moisture Content

The patches were weighed individually and then placed in a desiccator containing a suitable desiccant (such as calcium chloride) for 24 hours. After removal, the patches were reweighed, and the percentage moisture content was calculated.

Moisture Uptake

Pre-weighed patches were exposed to a controlled humidity environment (generally using a saturated salt solution) for 24 hours. The patches were then reweighed, and the percentage increase in weight was determined.

Fourier Transform Infrared (FT-IR) Analysis

FT-IR spectra of the pure drug and formulated patches were recorded to identify any possible chemical interactions between the drug and polymers. Characteristic peaks were compared to confirm compatibility.

In Vitro Drug Diffusion Study

Drug release from the patches was studied using a Franz diffusion cell. The patch was placed on a suitable membrane between the donor and receptor compartments. The receptor medium was maintained at a constant temperature with

continuous stirring. Samples were withdrawn at regular intervals up to 24 hours and replaced with fresh medium. The samples were analyzed spectrophotometrically, and cumulative drug release was calculated.

%Cumulative Drug Release= Amount of drug released /Total drug content ×100

Results and Discussion

Preformulation Studies of Drug

Table 2: Physicochemical Properties of Levetiracetam

S.No	Test	Results
1	Appearance	White to off-white powder
2	Odour	Odourless
3	Nature	Crystalline powder
4	Solubility	Freely soluble in water; soluble in acetonitrile, ethanol, and methanol
5	Category	Anticonvulsant (used for the treatment of epilepsy/seizures)
6	Melting Point	116 °C

Interpretation:

The observed physicochemical properties were consistent with reported standards, confirming the identity and purity of the drug. The melting point and solubility profile indicate suitability for transdermal formulation development.

Evaluation of Transdermal Patches

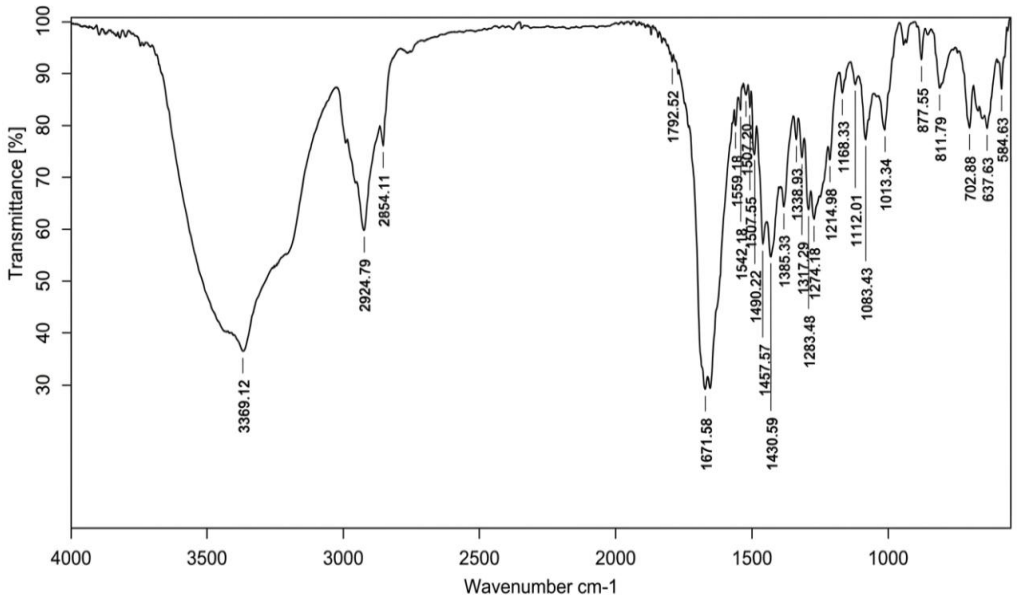

Figure 3: FT-IR spectra for Levetiracetam

Table 2: Evaluation Parameters of Formulations (LTP1–LTP5)

Formulations	Appearance	Weight Variation (mg)	Thickness (µm)	Folding Endurance	Moisture Content (%)	Moisture Uptake (%)	Drug Content (%)
LTP1	Slightly Opaque	518 ± 4	148.2 ±	145 ± 5	3.1 ± 0.4	7.2 ± 0.8	97.5 ± 0.6
LTP2	Clear, Smooth	506 ± 3	142.5 ±	162 ± 4	2.4 ± 0.3	6.1 ± 0.5	98.2 ± 0.5
LTP3	Smooth, Tough	512 ± 5	145.1 ±	158 ± 7	2.2 ± 0.4	5.8 ± 0.9	98.4 ± 0.3
LTP4	Clear, Flexible	498 ± 2	138.4 ±	172 ± 3	1.8 ± 0.2	4.8 ± 0.3	99.4 ± 0.1
LTP5	Clear, Flexible	502 ± 4	140.2 ±	168 ± 6	2.3 ± 0.5	5.4 ± 0.6	98.9 ± 0.4

Reported as mean ± S.D. (n=3)

In-vitro Drug Release Studies

Table 3: Cumulative Percentage Drug Release of Levetiracetam Transdermal Patches

Time (hr)	LTP 1 (%)	LTP 2 (%)	LTP 3 (%)	LTP 4 (%)	LTP 5 (%)
0	**0**	**0**	**0**	**0**	**0**
1	12.42	10.15	8.24	15.82	11.45
2	24.15	19.82	15.12	28.91	22.18
4	38.64	34.12	28.55	45.12	36.42
8	55.12	51.45	44.92	68.45	53.21
12	72.84	68.12	61.24	82.34	70.15
16	81.25	77.45	70.82	91.12	80.42
20	88.42	84.12	78.55	95.64	86.11
24	92.15	88.42	82.15	98.85	90.12

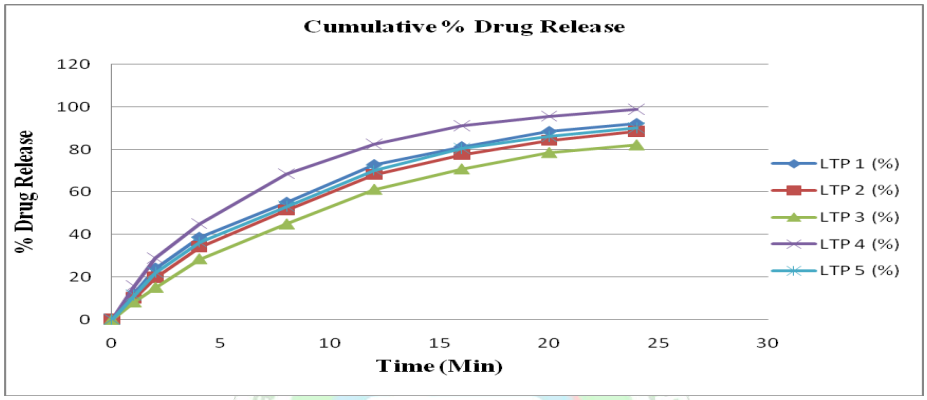

Figure 3: In vitro release profile of Levetiracetam Transdermal Patch (LTP1-LTP5)

RESULTS AND DISCUSSION

The in-vitro diffusion study confirmed that all transdermal formulations of Levetiracetam provided sustained drug release over a period of 24 hours. A steady increase in cumulative drug release was observed with time, indicating controlled diffusion from the polymeric matrix. At 24 hours, cumulative drug release was recorded as 92.15% (LTP1), 88.42% (LTP2), 82.15% (LTP3), 98.85% (LTP4), and 90.12% (LTP5). Among these, LTP4 demonstrated the highest release, which may be attributed to the optimized combination of natural and synthetic polymers. The presence of Ficus carica mucilage along with HPMC K100 and Eudragit S100 appears to have created a balanced matrix that supports effective drug diffusion. Formulations LTP1, LTP2, and LTP3 showed relatively slower release, possibly due to higher polymer concentration or lack of polymeric balance, which may have restricted drug movement within the matrix. LTP5 exhibited improved release compared to these formulations but remained slightly lower than LTP4, suggesting that equal proportions of polymers may not yield optimal performance.The absence of an initial burst effect and the gradual release pattern indicate that the drug release is primarily governed by diffusion. This behavior is characteristic of matrix-type transdermal systems designed for prolonged drug delivery.

CONCLUSION

Matrix-type transdermal patches of Levetiracetam were successfully developed using a combination of natural and synthetic polymers. All formulations showed acceptable physicochemical properties along with sustained drug release. Among the prepared batches, LTP4 was identified as the optimized formulation based on its superior drug release profile, mechanical properties, and stability characteristics. The formulation achieved a maximum drug release of 98.85% over 24 hours, indicating efficient and controlled delivery.The findings suggest that the incorporation of Ficus carica mucilage with HPMC K100 and Eudragit S100 offers a suitable approach for developing transdermal systems. This method may serve as an effective alternative to oral administration by providing prolonged drug release and improving patient compliance in epilepsy management.

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