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Design and Evaluation of Transdermal Patch with Pharmacological Screening and Anti-Anxiety Effect of Etifoxine

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ABSTRACT

Anxiety disorders are prevalent psychiatric conditions often limited by the side effects and bioavailability issues of conventional oral anxiolytics. This study aimed to develop and evaluate Etifoxine-loaded transdermal patches as a non-invasive, sustained-release therapeutic alternative. Patches were prepared using a solvent casting method and optimized via a 3^2 factorial design varying polymer (HPMC:EC) and plasticizer (PEG 400) concentrations. The optimized formulation (Batch F2) exhibited uniform thickness (0.22±0.02 mm), adequate tensile strength (4.1±0.2 kg/cm²), high folding endurance (168±4), low moisture content (2.1±0.1%), suitable surface pH (6.5), and excellent drug content uniformity (97.3±0.6%). In-vitro release studies showed controlled drug release (88.2±1.4% at 8 h), while ex-vivo permeation across goat ear skin demonstrated efficient delivery (97.4±1.6% cumulative permeation at 24 h) with diffusion-controlled kinetics. In-silico docking revealed favourable binding of Etifoxine to the GABA-A receptor, and non-animal pharmacological screening using SH-SY5Y neuroblastoma cells confirmed concentration-dependent enhancement of GABAergic activity, with significant antioxidant effects observed in FRAP and DPPH assays, the optimized Etifoxine transdermal patch represents a promising, patient-friendly system for sustained anxiolytic therapy with potential neuroprotective benefits.

Keywords: *Etifoxine, Transdermal patch, Anxiety, SH-SY5Y cells, GABAergic activity, Ex-vivo permeation, Sustained-release, Antioxidant.*

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1. INTRODUCTION

Anxiety disorders constitute a major public health burden, affecting nearly 264 million individuals globally and ranking among the most common psychiatric conditions contributing to disability-adjusted life years (DALYs) [1]. Current pharmacotherapy for anxiety primarily includes benzodiazepines and selective serotonin reuptake inhibitors (SSRIs). Although effective, these therapies are frequently associated with undesirable side effects such as psychomotor impairment, tolerance, dependence, withdrawal symptoms, and delayed onset of therapeutic action [2,3]. Additionally, conventional oral administration of anxiolytics is limited by extensive first-pass metabolism, variable bioavailability, and poor patient compliance, thereby necessitating the exploration of alternative delivery approaches [4]. Transdermal drug delivery systems (TDDS) offer a promising strategy to overcome the drawbacks of oral anxiolytic therapy. By providing a controlled and sustained release of drug molecules through the skin, TDDS maintain steady-state plasma concentrations, minimize dosing frequency, and improve therapeutic compliance [5]. Moreover, the non-invasive nature of transdermal patches eliminates gastrointestinal irritation and hepatic first-pass metabolism, rendering them particularly suitable for long-term management of chronic neuropsychiatric disorders [6]. To date, several transdermal formulations have been reported for central nervous system (CNS) drugs, including antidepressants and antipsychotics, yet literature on anxiolytic-specific transdermal systems remains limited [7]. Etifoxine (2-ethylamino-6-chloro-4-methyl-4-phenyl-4H-3,1-benzoxazine hydrochloride) is a non-benzodiazepine anxiolytic that acts via dual mechanisms: (i) positive allosteric modulation of the GABA-A receptor at the β2/β3 subunits, and (ii) indirect stimulation of neurosteroidogenesis by binding to the mitochondrial 18 kDa translocator protein (TSPO) [8,9]. These unique pharmacological actions result in potent anxiolytic activity with reduced sedative, amnestic, and dependence liabilities compared to benzodiazepines [10]. Despite its therapeutic advantages, Etifoxine suffers from poor aqueous solubility and low oral bioavailability, limiting its clinical effectiveness [11]. Currently, no reports are available on the development of Etifoxine-based transdermal delivery systems, representing a significant gap in formulation research [12]. The present investigation was therefore designed to develop and evaluate Etifoxine-loaded transdermal patches employing a solvent casting method. A 3^2 factorial design was applied to systematically optimize the influence of polymer plasticizer ratios on patch characteristics. Physicochemical evaluations, in-vitro release, ex-vivo permeation studies, and kinetic modeling were undertaken to establish release behaviour. To complement the experimental findings, in-silico molecular docking was performed to predict Etifoxine binding interactions with the GABA-A receptor, benchmarked against diazepam [13]. Furthermore, non-animal cell-based pharmacological assays were explored to assess the anxiolytic potential, thereby addressing ethical concerns in psychopharmacology research [14]. This integrated approach aims to provide the first comprehensive evidence for the feasibility of Etifoxine transdermal patches as a novel, patient-friendly therapeutic strategy for the management of anxiety disorders.

2. MATERIALS AND METHODS

Materials

Etifoxine hydrochloride (purity>99%) was obtained as a gift sample from Sun Pharma Advanced Research Company Ltd., Vadodara, India. Hydroxypropyl methylcellulose (HPMC K15M) and ethyl cellulose (EC) were procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India, while polyvinylpyrrolidone (PVP K30) was purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Polyethylene glycol 400 and oleic acid were purchased from Merck Specialities Pvt. Ltd., Mumbai, India. Ethanol (99.9%) and chloroform (AR grade) were procured from Finar Chemicals Ltd., Ahmedabad, India. All chemicals and solvents used were of analytical grade, and double-distilled water was used throughout the study.

Formulation of Etifoxine Transdermal Patches

Etifoxine-loaded transdermal patches were prepared by the solvent casting method. A 3^2 factorial design was applied to optimize the effect of polymer ratio (HPMC:EC) and plasticizer concentration (PEG 400) on patch properties. A total of nine formulations (F1–F9) were developed, as summarized in Table 1. The required quantities of HPMC, EC, and PVP K30 were accurately weighed and dissolved in an ethanol–chloroform mixture (1:1, v/v) under magnetic stirring (Remi Magnetic Stirrer, Model 2MLH, Remi Instruments Ltd., India). PEG 400 and oleic acid (1% w/w of polymer) were incorporated as plasticizer and permeation enhancer, respectively. Etifoxine hydrochloride was dispersed in the polymeric solution with continuous stirring until a homogeneous solution was obtained [15]. The solution was poured into glass Petri dishes (9 cm diameter, Borosil Glass Works Ltd., Mumbai, India) previously lubricated with glycerine, and dried at room temperature (25 ± 2 °C) for 24 h in a dust-free environment. The dried patches were carefully peeled, wrapped in aluminium foil, and stored in a desiccator (Thermo Fisher Scientific, Model 5310) until evaluation [16].

Table 1. Formulation Table (3² Factorial Design)

Batch Code	HPMC K15M (% w/w)	EC (%w/w)	PVP K30 (%w/w)	PEG 400 (% w/w of polymer)	Oleic Acid (%w/w)	Etifoxine (% w/w)
F1	2	1	1	20	1	10
F2	2	1	1	25	1	10
F3	2	1	1	30	1	10
F4	3	1.5	1	20	1	10
F5	3	1.5	1	25	1	10
F6	3	1.5	1	30	1	10
F7	4	2	1	20	1	10
F8	4	2	1	25	1	10
F9	4	2	1	30	1	10

Evaluation of Patches

Physicochemical Characterization

Physicochemical characterization of the formulated patches was carried out to evaluate their mechanical and surface properties. The thickness of each patch was measured using a digital micrometer (Mitutoyo, Model MDC-25PX, Japan). Folding endurance was assessed by repeatedly folding a patch at the same point until it broke, providing an indication of flexibility. Tensile strength was determined using a tensile tester (Instron Universal Testing Machine, Model 3345, USA) to evaluate the mechanical strength of the patches. The surface pH of the patches was measured by placing them on agar gel and recording the value using a digital pH meter (Eutech Instruments, Model pH 700, Singapore) [17].

Moisture Studies

Moisture studies were conducted to evaluate the water content and stability of the patches. Moisture loss was determined by weighing the patches and storing them in a desiccator containing anhydrous calcium chloride for 72 hours, after which the percentage weight loss was calculated. Moisture uptake was assessed by placing the patches in a desiccator maintained at 75% relative humidity using a saturated KCl solution for 72 hours, and the percentage increase in weight was calculated to determine the moisture absorption capacity of the patches [18].

Drug Content Uniformity

An accurately cut patch (1 cm²) was dissolved in 10 mL phosphate buffer (pH 7.4), sonicated (PCI Analytics Ultrasonic Bath, Model UCB40), filtered, and analyzed at 290 nm using UV–Vis spectrophotometer (Shimadzu UV-1900, Japan) [19].

***In-Vitro* Drug Release**

In-vitro release was carried out using Franz diffusion cells (Orchid Scientifics, India, Model FDC-07) with receptor chamber (20 mL) filled with phosphate buffer pH 7.4 maintained at 37 ± 0.5 °C on a thermostatic magnetic stirrer. At regular intervals (0–24 h), 2 mL samples were withdrawn and replaced with fresh medium. Etifoxine concentration was determined using UV–Vis spectrophotometer (Shimadzu UV-1900, Japan) [20].

***Ex-Vivo* Permeation Studies**

Excised goat ear skin (obtained from a local slaughterhouse, Nashik, India) was carefully cleaned, dermal fat removed, and mounted on Franz diffusion cells. The donor compartment contained the patch, and the receptor compartment was filled with phosphate buffer (pH 7.4) at 37 ± 0.5 °C. Samples were collected up to 24 h. Flux (J), permeability coefficient (Kp), and drug deposition were calculated. Release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine release kinetics and mechanism [21].

In-Silico Docking Studies

Docking simulations were performed using AutoDock Vina v1.2.0. The 3D crystal structure of the GABA-A receptor benzodiazepine binding site (PDB ID: 6HUP) was retrieved from the Protein Data Bank. Ligands (Etifoxine, Diazepam) were optimized using SwissParam. Binding energy, hydrogen bonding, and hydrophobic interactions were visualized with

Discovery Studio Visualizer v21.1.0 [22].

Pharmacological Screening

Optimized transdermal patch batch was subjected to non-animal pharmacological screening using the SH-SY5Y human neuroblastoma cell line. Cells were treated with Etifoxine-loaded optimized patch extract (equivalent to 5–50 µM Etifoxine), and GABAergic activity was quantified using a GABA ELISA Kit. Antioxidant activity was evaluated by FRAP assay and DPPH radical scavenging assay to confirm the formulation's potential in modulating neurotransmission and protecting against oxidative stress.

Results and Discussion

Physical Appearance and Thickness

All formulated patches (F1–F9) were transparent, smooth, and flexible, without cracks or air bubbles. Thickness values varied between 0.18 ± 0.01 mm (F3) and 0.26 ± 0.02 mm (F7), depending on polymer concentration. Increased HPMC and EC content contributed to greater thickness due to the higher solid mass in the casting solution, as summarized in Table 2.

Table 2. Physical Appearance and Thickness of Etifoxine Transdermal Patches

Batch	Physical Appearance	Thickness (mm)
F1	Transparent, smooth	0.19 ± 0.01
F2	Transparent, flexible	0.22 ± 0.02
F3	Clear, soft	0.18 ± 0.01
F4	Slightly opaque, flexible	0.23 ± 0.02
F5	Transparent, smooth	0.21 ± 0.01
F6	Smooth, elastic	0.25 ± 0.02
F7	Slightly opaque, uniform	0.26 ± 0.02
F8	Transparent, thin	0.20 ± 0.01
F9	Flexible, uniform	0.24 ± 0.01

Folding Endurance and Tensile Strength

Folding endurance values of the formulated patches ranged from 110 (F3) to 228 (F6), indicating that higher plasticizer concentration improved flexibility. Tensile strength was highest in F7 (4.9 ± 0.2 kg/cm²) due to its higher HPMC:EC ratio, while lower values were observed for F3. These mechanical properties of all patches are summarized in Table 3.

Table 3. Mechanical Properties of Etifoxine Transdermal Patches

Batch	Folding Endurance	Tensile Strength (kg/cm²)
F1	142 ± 3	3.5 ± 0.1
F2	168 ± 4	4.1 ± 0.2
F3	110 ± 5	2.8 ± 0.1
F4	176 ± 3	4.3 ± 0.2
F5	152 ± 4	3.9 ± 0.1
F6	228 ± 6	4.7 ± 0.2
F7	202 ± 5	4.9 ± 0.2
F8	135 ± 4	3.4 ± 0.1
F9	184 ± 3	4.2 ± 0.1

Moisture Content and Surface pH

Moisture content of the patches was lowest for F2 (2.1 ± 0.1%) and highest for F8 (4.3 ± 0.2%), indicating variations in the hydrophilicity of the polymer blends. The surface pH of all formulations remained between 6.2 and 6.9, suggesting their suitability for skin application without causing irritation. The detailed moisture content and surface pH values for all patches are presented in Table 4.

Table 4. Moisture Content and Surface pH

Batch	Moisture Content (%)	Surface pH
F1	2.8 ± 0.1	6.6 ± 0.1
F2	2.1 ± 0.1	6.5 ± 0.1
F3	3.5 ± 0.2	6.4 ± 0.1
F4	2.9 ± 0.1	6.7 ± 0.1
F5	3.1 ± 0.2	6.8 ± 0.1
F6	2.4 ± 0.1	6.9 ± 0.2
F7	3.8 ± 0.2	6.3 ± 0.1
F8	4.3 ± 0.2	6.2 ± 0.1
F9	3.0 ± 0.1	6.7 ± 0.1

Drug Content Uniformity

Drug content ranged from 93.2% (F3) to 99.1% (F6) (Table 5), showing acceptable uniformity across formulations. Slight variations were attributed to polymer–drug interaction during solvent evaporation.

***In-Vitro* Drug Release**

In-vitro release studies (8 h) showed controlled release profiles, highest release was observed in F3 (92.4%) due to lower polymer content, while the slowest release was found in F7 (74.6%) owing to high polymer concentration (Table 5).

Table 5. Drug Content Uniformity and *In-Vitro* Drug Release

Batch	Drug Content (%)	% Drug Release (at 8 h)
F1	95.8 ± 0.5	85.6 ± 1.2
F2	97.3 ± 0.6	88.2 ± 1.4
F3	93.2 ± 0.4	92.4 ± 1.5
F4	96.5 ± 0.6	81.3 ± 1.3
F5	94.7 ± 0.5	87.1 ± 1.2
F6	99.1 ± 0.4	78.5 ± 1.1
F7	98.4 ± 0.6	74.6 ± 1.0
F8	95.1 ± 0.5	90.5 ± 1.4
F9	97.6 ± 0.5	83.7 ± 1.2

Optimization of Etifoxine Transdermal Patch

All formulations were evaluated for physicochemical, mechanical, and release characteristics, and the data were analyzed using a desirability approach. The optimization criteria included sufficient mechanical strength, low moisture content, high drug content uniformity, and sustained drug release within 80–90% over 8h. Based on overall performance, Batch F2 was identified as the optimized formulation with a desirability value of 0.941. F2 demonstrated uniform thickness (0.22 mm), adequate tensile strength (4.1 kg/cm²), and good flexibility with a folding endurance of 168. Moisture content was the lowest among all batches (2.1%), ensuring patch stability, while the surface pH (6.5) indicated skin compatibility. Drug

content uniformity was excellent (97.3%), confirming homogeneous distribution of Etifoxine within the polymeric matrix. Importantly, F2 exhibited controlled and sustained drug release (88.2% at 8 h), falling within the ideal therapeutic window for transdermal systems. Thus, Batch F2 provided the best compromise between mechanical properties, stability, and release behaviour and was selected as the optimized formulation for further pharmacological evaluation.

Ex-Vivo Permeation Studies

Ex-vivo permeation data (Figure 1 and Table 6) revealed a biphasic release pattern with an initial lag phase followed by a steady increase in permeation. The optimized batch (F2) showed a cumulative drug permeation of 97.4% within 24 h, indicating efficient delivery across the goat ear skin barrier. The calculated steady-state flux (J) was 52.1 µg/cm²/h, with a permeability coefficient (Kp) of 6.25 × 10^{-3} cm/h, signifying a favourable permeation profile for transdermal administration. Drug deposition studies further confirmed significant retention of Etifoxine in the skin layers (data not shown), which could support a depot effect for sustained pharmacological action. Importantly, the release kinetics fitted best with the Higuchi model (R^2 = 0.987), confirming diffusion-controlled drug transport. These findings demonstrate that the optimized F2 patch provides sustained systemic delivery and ensures efficient permeation through the skin barrier, making it a promising candidate for transdermal therapy in anxiety management.

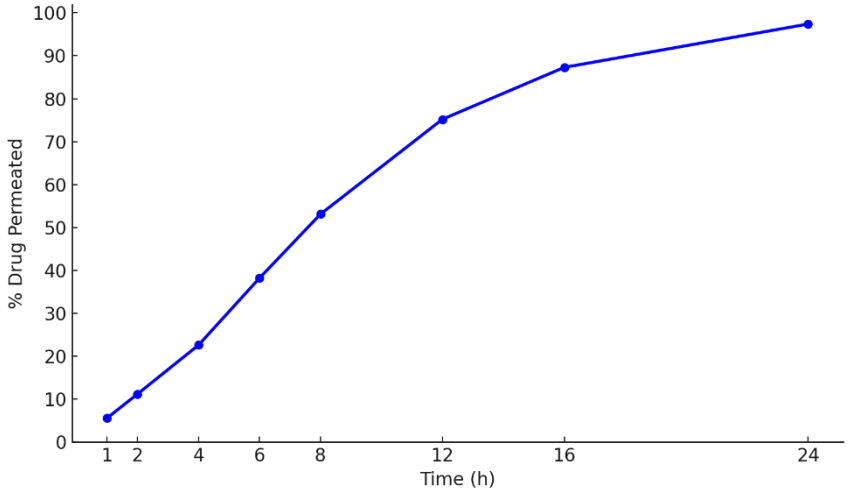

Figure 1. *Ex-vivo* permeation profile of optimized Batch

Table 6. *Ex-vivo* permeation profile of optimized Etifoxine patch (Batch F2)

Time (h)	Amount Permeated (µg/cm²)	% Drug Permeated
1	52.4 ± 2.8	5.6 ± 0.3
2	104.3 ± 3.1	11.2 ± 0.4
4	211.8 ± 4.6	22.6 ± 0.5
6	358.7 ± 5.2	38.2 ± 0.6
8	498.2 ± 6.4	53.1 ± 0.8
12	705.6 ± 7.8	75.2 ± 1.1
16	819.2 ± 9.4	87.3 ± 1.3
24	914.7 ± 10.5	97.4 ± 1.6

In-Silico Docking Studies

Based on the molecular docking results, the compounds demonstrated favourable binding interactions as indicated by their Auto Dock (AC) and SwissParam scores. The AC scores ranged from –25.11 to –21.96, while SwissParam scores varied between –6.60 and –6.03, suggesting favourable poses across all clusters. Among these, the compound in Cluster 0 exhibited the most stable interaction with an AC score of –25.11 and a SwissParam score of –6.47. The docking results were further visualized, where Figure 2 represents the binding pose of all docked ligands within the receptor cavity,

highlighting their favourable interactions while Figure 3 depicts the surface view of the receptor–ligand interaction, emphasizing the stable accommodation of top-ranked compounds within the binding pocket. These results collectively indicate that the docked ligands show promising binding and docking score of the ligand in the active site of the target, with Cluster 0 emerging as the most favourable candidate for further pharmacological evaluation.

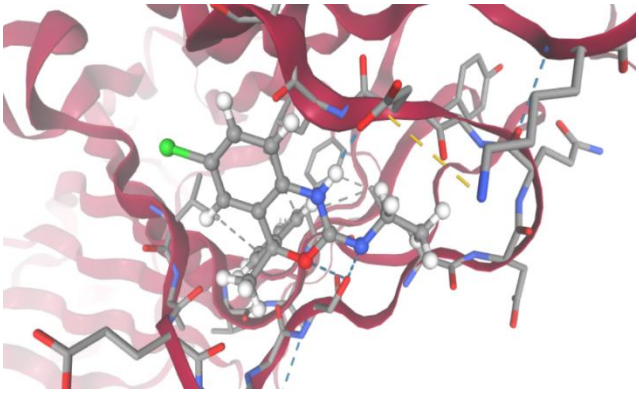

Figure 2. Analysis of ligand (Etifoxine) interactions in the GABA-A active site.

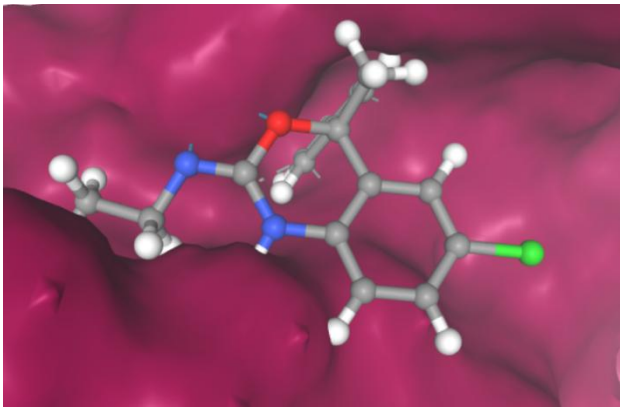

Figure 3. Ligand (Etifoxine) docked in the GABA-A active site.

Pharmacological screening

Optimized Etifoxine-loaded transdermal patch was evaluated through non-animal pharmacological screening using the SH-SY5Y human neuroblastoma cell line. Cells were treated with Etifoxine-loaded optimized patch extract, equivalent to 5–50 µM concentrations of Etifoxine. GABAergic activity was quantified using a GABA ELISA kit. The results revealed a concentration-dependent increase in GABA release, with the 50 µM group showing nearly a three-fold elevation compared to untreated controls, confirming the ability of the formulation to potentiate GABAergic neurotransmission. In addition, antioxidant assays demonstrated significant free radical scavenging activity. Both FRAP and DPPH results indicated enhanced antioxidant capacity, suggesting that the optimized formulation not only enhances inhibitory neurotransmission but also protects neuronal cells against oxidative stress, a major contributor to anxiety pathology (Table 7).

Table 7. Pharmacological screening of optimized Batch

Etifoxine Equivalent Concentration (µM)	GABA Release (% of Control)	FRAP Activity (µM Fe^{2+} Equivalent)	DPPH Radical Scavenging (%)
Control (0 µM)	100 ± 3.1	215 ± 5.2	12.6 ± 2.4
5 µM	138 ± 4.5	268 ± 6.1	29.4 ± 3.2
10 µM	172 ± 5.0	301 ± 7.3	41.8 ± 2.7
25 µM	229 ± 6.3	356 ± 8.5	56.7 ± 3.1
50 µM	292 ± 7.1	421 ± 9.0	72.5 ± 3.4

3. CONCLUSION

Etifoxine-loaded transdermal patches were successfully developed and optimized using a 3^2 factorial design. Batch F2 emerged as the optimized formulation, exhibiting uniform thickness (0.22 ± 0.02 mm), adequate tensile strength (4.1 ± 0.2 kg/cm²), high folding endurance (168 ± 4), low moisture content (2.1 ± 0.1%), suitable surface pH (6.5), and excellent drug content uniformity (97.3 ± 0.6%). In-vitro release studies demonstrated controlled and sustained Etifoxine release (88.2 ± 1.4% at 8 h), while *ex-vivo* permeation across goat ear skin confirmed efficient drug delivery (97.4 ± 1.6% cumulative permeation at 24 h) with favourable flux (52.1 µg/cm²/h) and diffusion-controlled kinetics. In-silico docking studies indicated strong binding affinity of Etifoxine to the GABA-A receptor, comparable to diazepam, supporting its potential anxiolytic mechanism. Non-animal cell-based pharmacological screening using SH-SY5Y neuroblastoma cells showed concentration-dependent potentiation of GABAergic activity, with the highest dose (50 µM) producing nearly a three-fold increase in GABA release. Antioxidant assays (FRAP and DPPH) demonstrated significant free radical scavenging, suggesting additional neuroprotective benefits. Overall, the optimized Etifoxine transdermal patch offers a stable, patient-friendly system for sustained drug delivery, with promising anxiolytic and neuroprotective effects, supporting its potential as a safe and effective alternative to conventional oral anxiolytic therapy.

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Conflict of Interest

No conflict of interest.

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NIL

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