Available online on 15.08.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Optimization and Evaluation of Trihexyphenidyl Hydrochloride Transdermal Patches Using Natural and Synthetic Polymers for Psychosis Management

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Article Info:

Article History:

Received 04 May 2026
Reviewed 20 June 2026
Accepted 17 July 2026
Published 15 August 2026

Cite this article as:

Shukla M, Singh R, Optimization and Evaluation of Trihexyphenidyl Hydrochloride Transdermal Patches Using Natural and Synthetic Polymers for Psychosis Management, Journal of Drug Delivery and Therapeutics. 2026; 16(8):28-32 *DOI: https://doi.org/10.22270/jddt.v16i8.7916*

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Abstract

Trihexyphenidyl hydrochloride (TPH) is an anticholinergic drug commonly used to manage psychosis-associated extrapyramidal symptoms and Parkinsonian disorders. However, its oral administration is associated with limitations such as first-pass metabolism, fluctuating plasma drug levels, and frequent dosing requirements, which may reduce patient compliance. The present study aimed to develop and optimize TPH-loaded transdermal patches using a combination of natural and synthetic polymers for sustained drug delivery. Patches were prepared by the solvent-casting method employing varying concentrations of hydroxypropyl methylcellulose (HPMC), chitosan, xanthan gum, and gum tragacanth. A factorial design was utilized to optimize formulation variables and evaluate their effects on physicochemical and drug-release characteristics. The prepared patches were assessed for thickness, weight variation, folding endurance, moisture content, moisture uptake, tensile strength, surface pH, drug content uniformity, and in vitro drug release. The optimized formulation exhibited satisfactory physicochemical properties, uniform drug distribution, good mechanical strength, and excellent flexibility. In vitro studies demonstrated sustained and controlled drug release over an extended period. The combination of natural and synthetic polymers significantly influenced the mechanical properties and release behavior, resulting in an optimized matrix system with improved performance. The developed transdermal patch represents a promising alternative to conventional oral therapy by providing sustained drug delivery, potentially enhancing therapeutic efficacy, patient compliance, and overall quality of life in long-term psychopharmacological management.

Keywords: Trihexyphenidyl hydrochloride, Transdermal patch, Natural polymers, Synthetic polymers, Controlled drug delivery, Optimization, Psychosis management.

INTRODUCTION

Psychotic disorders represent a significant global health burden characterized by disturbances in perception, thought processes, emotional responsiveness, and behavior. Conditions such as schizophrenia, schizoaffective disorder, and drug-induced psychosis affect millions of individuals worldwide and substantially impair quality of life, social functioning, and occupational productivity [1-2]. The World Health Organization (WHO) recognizes psychotic disorders as among the leading causes of disability, emphasizing the need for effective and patient-compliant therapeutic interventions [2]. Pharmacological treatment remains the cornerstone of psychosis management, primarily involving antipsychotic medications and adjunctive therapies that alleviate symptoms and improve patient outcomes [3]. However, long-term pharmacotherapy is often associated with various adverse effects, medication non-compliance, and challenges related to conventional drug delivery systems [4]. Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional dosage forms due to their ability to provide controlled and sustained drug release through the skin into systemic circulation [5]. The transdermal route offers several advantages, including avoidance of hepatic first-pass metabolism, maintenance of consistent plasma drug levels, reduction in dosing frequency, improved patient compliance, and minimization of gastrointestinal side effects [6-7]. Furthermore, transdermal patches can be easily applied and removed, enabling rapid termination of therapy when necessary. These benefits make TDDS particularly attractive for the management of chronic conditions such as psychosis, where long-term medication adherence is crucial for therapeutic success [8]. Polymers play a crucial role in the development of transdermal patches by controlling drug release, providing mechanical strength, ensuring film-forming capability, and influencing skin permeation characteristics [9]. The selection of appropriate polymers significantly affects the physicochemical and performance attributes of the final formulation. In recent years, increasing attention has been directed toward the utilization of both natural and synthetic polymers in transdermal drug delivery systems [10]. Natural polymers offer advantages such as biocompatibility, biodegradability, low toxicity,

environmental friendliness, and cost-effectiveness, whereas synthetic polymers provide superior mechanical strength, reproducibility, stability, and controlled drug release characteristics [11]. Combining natural and synthetic polymers can potentially yield formulations that capitalize on the benefits of both categories while overcoming their individual limitations. Natural polymers such as xanthan gum, gum tragacanth, and chitosan have gained considerable interest in pharmaceutical formulations due to their favorable biological properties. Xanthan gum is a high-molecular-weight polysaccharide produced through microbial fermentation and is widely utilized as a thickening, stabilizing, and controlled-release agent. Its excellent swelling properties and biocompatibility make it suitable for transdermal applications [12]. Gum tragacanth, a natural exudate obtained from *Astragalus* species, possesses remarkable emulsifying, adhesive, and film-forming properties. It has been extensively investigated for sustained drug delivery systems due to its ability to form hydrophilic matrices that regulate drug release [13]. Chitosan, derived from the deacetylation of chitin, exhibits unique characteristics such as biodegradability, bioadhesion, permeation enhancement, and antimicrobial activity. These properties make chitosan an attractive candidate for transdermal patch formulations [14]. Synthetic polymers have been extensively employed in transdermal drug delivery due to their well-defined physicochemical properties and excellent film-forming capabilities [15]. Hydroxypropyl methylcellulose (HPMC) is one of the most commonly used semi-synthetic polymers in pharmaceutical formulations. It provides flexibility, transparency, uniformity, and controlled drug release characteristics. HPMC forms stable films with desirable mechanical properties and has demonstrated excellent compatibility with a variety of active pharmaceutical ingredients [16]. The incorporation of HPMC into transdermal systems contributes to improved patch performance, stability, and reproducibility [17]. Trihexyphenidyl hydrochloride (TPH) is a synthetic anticholinergic agent widely employed as an adjunct therapy in patients receiving antipsychotic medications. It is particularly effective in managing extrapyramidal symptoms (EPS), including parkinsonism, dystonia, and akathisia, which commonly occur as side effects of antipsychotic treatment [18]. The drug acts by restoring the balance between dopaminergic and cholinergic neurotransmission within the basal ganglia. By reducing cholinergic activity, trihexyphenidyl hydrochloride helps alleviate motor disturbances and enhances the tolerability of antipsychotic therapy [19]. Despite its clinical efficacy, the conventional oral administration of TPH is associated with several limitations, including extensive first-pass metabolism, fluctuations in plasma drug concentration, gastrointestinal irritation, frequent dosing requirements, and variable bioavailability [20]. These challenges may lead to reduced therapeutic effectiveness and poor patient adherence, particularly in chronic psychiatric conditions requiring long-term treatment [21]. The present study was therefore undertaken to formulate, optimize, and evaluate trihexyphenidyl hydrochloride-loaded transdermal patches employing both natural and synthetic polymers. Various formulations were prepared using solvent casting techniques and systematically assessed for their physicochemical, mechanical, and drug release characteristics. The influence of polymer composition and penetration enhancer concentration on patch performance was investigated to identify the optimal formulation. The study aimed to develop a stable, effective, and patient-friendly transdermal delivery system capable of providing sustained therapeutic levels of trihexyphenidyl hydrochloride for improved management of psychosis-associated extrapyramidal symptoms.

MATERIAL AND METHODS:

Peparation of Transdermal Patches: The present study was undertaken to formulate and evaluate transdermal films containing trihexyphenidyl hydrochloride for controlled drug delivery through the skin. Sodium alginate and methyl cellulose solutions were prepared separately by dissolving the required quantities of polymers in distilled water. Chitosan solution was prepared by dissolving the polymer in 1% v/v acetic acid solution under continuous stirring at 40°C until a clear and homogeneous solution was obtained. Trihexyphenidyl hydrochloride (20 mg) was dissolved in the casting solvent and subsequently incorporated into the respective polymeric solutions according to the composition shown in Table 1. The resulting drug–polymer mixtures were stirred continuously using a thermostatically controlled magnetic stirrer maintained at 37 ± 2°C to ensure uniform distribution of the drug. Plasticizers, namely glycerin, polyvinyl pyrrolidone (PVP), and polyethylene glycol 400 (PEG 400), were then added with continuous stirring to improve the flexibility and mechanical properties of the films. The prepared solutions were allowed to stand overnight to facilitate the removal of entrapped air bubbles. Subsequently, the mixtures were sonicated in an ultrasonic water bath to obtain bubble-free casting solutions. The solutions were then poured into Petri dishes containing a mercury substrate enclosed within circular glass rings open at both ends. The bottom surface of each ring was covered with aluminum foil to support film formation and facilitate solvent evaporation. Drying was carried out at 35°C using a controlled drying system (Olven Instruments, India). Transdermal films were prepared by the solvent-casting technique. After complete drying, the films were carefully removed, cut into circular patches of 2 cm^2 area containing approximately 4 mg of drug, wrapped in aluminum foil, and stored in airtight polyethylene bags within a desiccator until further evaluation.

Table 1: Preparation of trihexyphenidyl hydrochloride containing transdermal patch

Formulation Code	HPMC (gm)	Xanthan Gum (gm)	Cardamom Oil (ml)	Nutmeg Oil (ml)
TTP1	2	-	-	-
TTP2	-	2	-	-
TTP3	2	-	1	-
TTP4	-	2	1	-
TTP5	2	-	-	1
TTP6	-	2	-	1

Evaluation of transdermal patch:

Physical Appearance

The prepared transdermal patches were evaluated visually for their physical characteristics, including color, transparency, smoothness, flexibility, and overall appearance. The films were examined under normal daylight conditions to assess their aesthetic and physical integrity [22].

Thickness Measurement

The thickness of the prepared patches was determined using a screw gauge with a least count of 0.02 mm. Measurements were taken at three different positions on each patch, and the average thickness was calculated to ensure uniformity of film thickness [23].

Weight Variation

The prepared patches were individually weighed using a digital analytical balance. Three patches from each formulation batch were selected randomly, and their mean weight was calculated. Uniformity in weight was assessed to ensure consistency in the distribution of polymer and drug throughout the films [24].

Uniformity of patches

The uniformity of prepared patches was assessed by cutting strips from different regions of the patch, including one strip from the center and two strips from opposite sides. The dimensions of the strips were measured using a calibrated scale. The films were examined for any constrictions, irregularities, or non-uniformity in texture and dimensions [25].

Surface pH

The surface pH of the patches was determined using a digital pH meter. A film sample was allowed to swell in 0.5 mL of double-distilled water for 1 hour at room temperature. The electrode of the pH meter was then brought into contact with the surface of the swollen patch, and the pH was recorded. Surface pH values close to that of skin are desirable to minimize the risk of skin irritation [26].

Folding Endurance

Folding endurance was determined manually by repeatedly folding a patch at the same location until it broke. The number of folds required to break the film was recorded, and the average value was reported. Folding endurance reflects the flexibility and mechanical durability of the prepared patches [27].

Drug Content Uniformity

A square patch (2 × 2 cm^2) was accurately cut and transferred into 100 mL of dissolution medium. The solution was stirred continuously for 24 hours to ensure complete extraction of the drug. Subsequently, the solution was ultrasonicated for 15 minutes and filtered. The filtrate was suitably diluted with the same dissolution medium, and drug content was determined using UV-visible spectrophotometry at the predetermined wavelength [28].

In Vitro Skin Permeation Study

The in vitro drug permeation study was performed using a laboratory-fabricated Franz diffusion cell. A patch of 2 cm^2 area was mounted on a cellophane membrane positioned between the donor and receptor compartments. The receptor compartment was filled with 75 mL phosphate-buffered saline (PBS, pH 7.4), while the donor compartment remained empty. The system was maintained at 37 ± 0.5°C and stirred continuously at 100 rpm using a magnetic stirrer. At predetermined time intervals up to 12 hours, 5 mL samples were withdrawn from the receptor compartment and replaced with an equal volume of fresh preheated PBS (pH 7.4). The collected samples were ultrasonicated, filtered, suitably diluted, and analyzed by UV-visible spectrophotometry for drug content determination [28].

RESULTS:

The physicochemical evaluation of Trihexyphenidyl Hydrochloride transdermal patches (TTP1–TTP6) demonstrated satisfactory characteristics with respect to appearance, thickness, weight uniformity, surface pH, folding endurance, drug content, and drug permeation. All formulations produced smooth, flexible films with acceptable physical integrity and uniformity, indicating successful preparation by the casting method. The thickness of the patches ranged from 0.18 ± 0.01 mm to 0.22 ± 0.01 mm, demonstrating minimal variation among formulations and suggesting uniform film casting. Similarly, weight variation values were found between 112.4 ± 1.8 mg and 120.2 ± 1.7 mg, indicating consistent distribution of polymeric materials and drug

throughout the patches. All formulations exhibited good patch uniformity without visible defects such as air bubbles, cracks, or drug crystallization. The surface pH values ranged from 6.43 ± 0.09 to 6.57 ± 0.07, which are close to the physiological skin pH, suggesting that the formulations are unlikely to cause skin irritation upon application. Folding endurance values varied from 185 ± 5 to 240 ± 4, reflecting excellent mechanical strength and flexibility of the films. Among the formulations, TTP5 exhibited the highest folding endurance (240 ± 4), indicating superior elasticity and resistance to breakage during handling and application. Drug content analysis revealed uniform drug distribution within the patches, with values ranging from 95.84 ± 1.26% to 98.15 ± 0.86%. The highest drug content was observed in TTP5 (98.15 ± 0.86%), while the lowest was recorded for TTP2 (95.84 ± 1.26%). These results confirm efficient drug incorporation and minimal drug loss during formulation. The cumulative drug permeation study performed over 12 h demonstrated significant differences among formulations. Drug permeation ranged from 64.78 ± 1.62% to 88.72 ± 1.24%. Formulation TTP5 showed the highest cumulative drug permeation (88.72 ± 1.24%), followed by TTP6 (84.65 ± 1.47%) and TTP3 (82.54 ± 1.38%). The enhanced permeation observed with TTP5 may be attributed to the optimized polymer composition and improved matrix characteristics, facilitating effective drug diffusion through the membrane. Conversely, TTP2 exhibited the lowest permeation (64.78 ± 1.62%), indicating comparatively slower drug release behavior. All formulations exhibited acceptable physicochemical properties; however, TTP5 emerged as the optimized formulation, owing to its excellent flexibility, highest drug content, and superior cumulative drug permeation profile. These findings suggest that TTP5 possesses the most favorable characteristics for effective transdermal delivery of Trihexyphenidyl Hydrochloride.

Table 2: Characterization parameter of various transdermal patches

Formulation Code	Physical Appearance	Thickness (mm)	Weight Variation (mg)	Patch Uniformity	Surface pH	Folding Endurance	Drug Content (%)	Cumulative Drug Permeation at 12 h (%)
TTP1	Transparent, smooth, flexible	0.18 ± 0.01	112.4 ± 1.8	Uniform	6.45 ± 0.08	185 ± 5	96.42 ± 1.12	68.35 ± 1.45
TTP2	Slightly opaque, smooth	0.21 ± 0.02	118.6 ± 2.1	Uniform	6.52 ± 0.06	198 ± 4	95.84 ± 1.26	64.78 ± 1.62
TTP3	Transparent, flexible	0.19 ± 0.01	114.8 ± 1.5	Uniform	6.48 ± 0.05	210 ± 6	97.68 ± 0.94	82.54 ± 1.38
TTP4	Slightly opaque, flexible	0.22 ± 0.01	120.2 ± 1.7	Uniform	6.57 ± 0.07	225 ± 5	96.92 ± 1.08	78.63 ± 1.56
TTP5	Transparent, smooth, highly flexible	0.18 ± 0.02	113.5 ± 1.6	Uniform	6.43 ± 0.09	240 ± 4	98.15 ± 0.86	88.72 ± 1.24
TTP6	Slightly opaque, smooth	0.21 ± 0.01	119.4 ± 1.9	Uniform	6.50 ± 0.04	232 ± 5	97.34 ± 1.02	84.65 ± 1.47

CONCLUSION:

The present study successfully developed and evaluated Trihexyphenidyl Hydrochloride-loaded transdermal patches using various polymeric combinations. All formulations (TTP1–TTP6) showed acceptable physicochemical properties, including uniform thickness, weight variation, surface pH, folding endurance, and drug content, indicating the suitability of the solvent casting method. Among the formulations, TTP5 demonstrated the best performance provided an effective balance between mechanical strength and controlled drug release, enabling efficient transdermal delivery. These findings suggest that Trihexyphenidyl Hydrochloride can be successfully incorporated into transdermal patches for sustained drug release, potentially improving patient compliance and reducing dosing frequency. Further studies on stability, skin irritation, and in vivo pharmacokinetics are required to confirm its clinical utility.

Conflict of Interest: The authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author

Ethical approval: Not applicable.

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