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Formulation And Evaluation of Transdermal Patch of Promethazine Hydrochloride

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ABSTRACT:

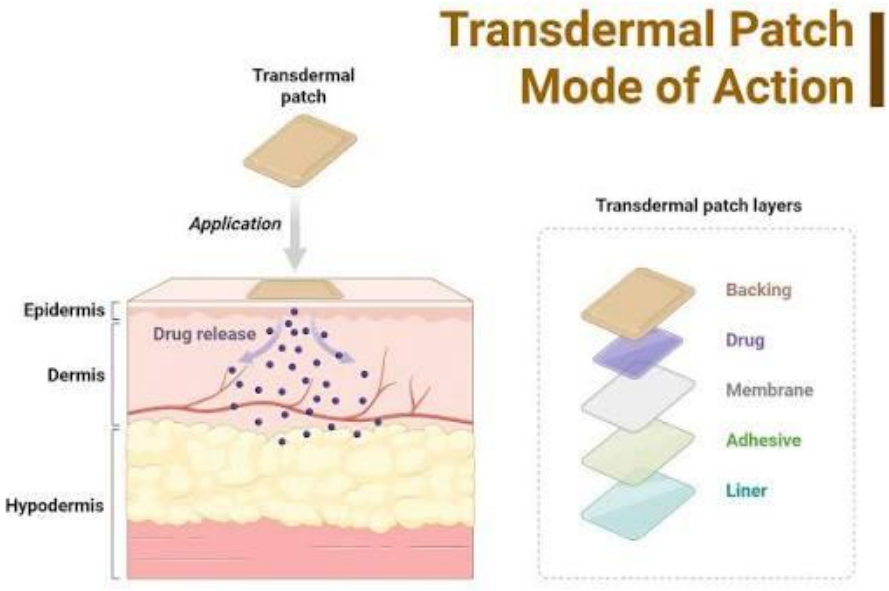
Transdermal drug delivery systems (TDDS) have emerged as an effective alternative to conventional oral dosage forms by providing controlled drug release, improving bioavailability, and bypassing hepatic first-pass metabolism. The present study aimed to formulate and evaluate matrix-type transdermal patches of Promethazine Hydrochloride using the solvent casting method. Hydroxypropyl methylcellulose (HPMC E15) was employed as the film-forming polymer, polyethylene glycol 400 (PEG 400) as the plasticizer, propylene glycol as the permeation enhancer, and glycerine as the flexibility enhancer. Three formulations (F1–F3) were developed by varying the concentrations of polymer and plasticizer while maintaining a constant drug content. The prepared patches were evaluated for physical appearance, thickness, weight variation, drug content, moisture content, and surface pH. Among the developed formulations, F1 containing 500 mg HPMC E15, 0.5 mL PEG 400, 0.5 mL propylene glycol, and 0.3 mL glycerine exhibited optimum physicochemical characteristics. The optimized patch

showed a smooth and flexible appearance, uniform thickness (0.318 ± 0.003 mm), low weight variation (%RSD 0.47%), high drug content (97.83 ± 0.36%), low moisture content (1.91 ± 0.04%), and a skin-compatible surface pH (6.17 ± 0.15). In contrast, formulations with lower polymer concentration produced sticky films, whereas higher polymer concentration resulted in brittle and cracked patches. The findings indicate that HPMC E15-based transdermal patches of Promethazine Hydrochloride possess suitable physicochemical properties and offer a promising approach for sustained drug delivery while overcoming the limitations associated with oral administration. Further studies on in vitro drug release, ex vivo skin permeation, stability, and pharmacokinetic evaluation are warranted to establish their clinical potential.

INTRODUCTION:

Transdermal drug delivery systems (TDDS) have gained considerable attention as an alternative to conventional oral and parenteral drug delivery methods because they provide controlled and sustained drug release while avoiding the limitations associated with gastrointestinal absorption and hepatic first-pass metabolism. In a transdermal system, the drug is delivered across the intact skin into the systemic circulation at a predetermined rate, thereby maintaining relatively constant plasma drug concentrations for an extended period. Compared with oral dosage forms, transdermal patches improve patient compliance by reducing dosing frequency, minimizing gastrointestinal irritation, and allowing therapy to be discontinued simply by removing the patch. These advantages have led to the successful commercialization of transdermal therapeutic systems for drugs such as nitroglycerin, fentanyl, nicotine, clonidine, estradiol, and scopolamine. Despite these benefits, the effectiveness of TDDS depends largely on the physicochemical properties of the drug and the barrier function of the stratum corneum, which is the principal obstacle to transdermal permeation. Drugs with low molecular weight, moderate lipophilicity, and high potency are generally considered suitable candidates for transdermal administration.[1]

The skin is the largest organ of the human body, covering approximately 1.7–2.0 m² of surface area, and serves as a protective barrier against physical, chemical, and microbial insults. Structurally, the skin comprises the epidermis, dermis, and hypodermis, with the outermost layer of the epidermis, the stratum corneum, providing the greatest resistance to drug permeation. The "brick-and-mortar" arrangement of corneocytes embedded within a lipid matrix restricts the passage of most therapeutic agents. Consequently, various formulation strategies, including the use of permeation enhancers, polymeric matrices, and optimized solvent systems, have been investigated to improve transdermal drug transport. Among these approaches, matrix-type transdermal patches prepared by the solvent casting method have gained widespread acceptance due to their ease of preparation, uniform drug distribution, scalability, and reproducibility.[1-3]



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Promethazine Hydrochloride is a first-generation H1-antihistamine belonging to the phenothiazine class and is extensively prescribed for the prevention and treatment of nausea, vomiting, motion sickness, allergic disorders, and preoperative sedation. Although Promethazine Hydrochloride is rapidly absorbed following oral administration, its clinical efficacy is significantly limited by extensive hepatic first-pass metabolism, resulting in an oral bioavailability of approximately 25%. Furthermore, repeated oral administration may produce undesirable adverse effects, including excessive sedation, dizziness, anticholinergic effects, and gastrointestinal discomfort. Therefore, an alternative drug delivery system capable of bypassing hepatic metabolism and maintaining prolonged therapeutic plasma concentrations would offer significant therapeutic benefits.[4]

Transdermal administration of Promethazine Hydrochloride represents a promising strategy to overcome these limitations. The drug possesses several physicochemical characteristics favorable for transdermal delivery, including a molecular weight of 320.88 g/mol and a lipophilicity (log P ≈ 4.18), which facilitate diffusion across the skin barrier. Delivering Promethazine Hydrochloride through a transdermal patch is expected to improve bioavailability, reduce fluctuations in plasma drug concentration, minimize dose-dependent adverse effects, and enhance patient compliance, particularly in patients experiencing nausea or vomiting who may have difficulty swallowing oral medications. Sustained transdermal delivery may also decrease the frequency of administration and improve therapeutic outcomes.[1,3,4]

The performance of a transdermal patch depends largely on the selection of suitable polymers, plasticizers, permeation enhancers, and solvents. Hydroxypropyl methylcellulose (HPMC E15) is a widely used hydrophilic polymer owing to its excellent film-forming ability, biocompatibility, non-toxicity, and mechanical strength. Polyethylene glycol 400 (PEG 400) functions as a plasticizer that improves film flexibility by reducing polymer rigidity, while glycerine enhances elasticity and moisture retention within the polymeric matrix. Propylene glycol serves both as a co-solvent and a chemical permeation enhancer by disrupting the lipid organization of the stratum corneum, thereby facilitating drug diffusion through the skin. The solvent casting technique offers a simple, economical, and reproducible method for preparing uniform matrix films with desirable physicochemical properties.[4,5]

The present study was therefore undertaken to formulate and evaluate matrix-type transdermal patches of Promethazine Hydrochloride using HPMC E15 as the film-forming polymer by the solvent casting method. Different formulations were prepared by varying the concentrations of polymer and plasticizer to optimize film characteristics. The prepared patches were evaluated for their physical appearance, thickness, weight variation, drug content, moisture content, and surface pH to identify the optimized formulation possessing suitable physicochemical properties for transdermal drug delivery. The study aims to provide a simple, stable, and effective transdermal formulation of Promethazine Hydrochloride that may serve as a potential alternative to conventional oral therapy.[1-4]

2. MATERIALS AND METHODS

2.1 Materials

Promethazine Hydrochloride was used as the model drug for the preparation of transdermal patches. Hydroxypropyl methylcellulose (HPMC E15) served as the film-forming polymer, polyethylene glycol 400 (PEG 400) was used as the plasticizer, propylene glycol as the permeation enhancer, and glycerine as the flexibility enhancer. Ethanol (95%) and distilled water were employed as co-solvents for dissolving the drug and polymer, respectively. Oleic acid and sodium carboxymethyl cellulose (CMC) were also used during formulation development. All chemicals and reagents were of analytical reagent (AR) grade and were used without further purification.

2.2 Equipment

The equipment used during formulation and evaluation included an analytical balance for accurate weighing of ingredients, a magnetic stirrer with heating facility for polymer dissolution, glass Petri dishes for casting the films, a digital micrometer screw gauge for thickness measurement, a UV-Visible spectrophotometer for drug content estimation, universal pH paper for surface pH determination, a hot air oven for moisture content analysis, and a desiccator containing silica gel for storage of the prepared patches.

2.3 Preparation of Transdermal Patches [3]

Promethazine Hydrochloride transdermal patches were prepared by the solvent casting method. Initially, the

required quantity of HPMC E15 was gradually dispersed in distilled water under continuous stirring for approximately 20 minutes. The dispersion was gently heated to approximately 40°C until a clear and homogeneous polymeric solution was obtained.

Separately, 100 mg of Promethazine Hydrochloride was dissolved in 5 mL of ethanol (95%). Polyethylene glycol 400, propylene glycol, and glycerine were subsequently added to the drug solution with continuous stirring to obtain a uniform mixture.

The polymeric solution was then added slowly to the drug solution under continuous stirring to produce a homogeneous casting solution. The resulting solution was allowed to stand undisturbed for approximately 30 minutes to remove entrapped air bubbles.

The bubble-free solution was carefully poured into leveled glass Petri dishes (90 mm diameter) and allowed to dry at room temperature for 24 hours. After complete solvent evaporation, the dried films were carefully peeled from the Petri dishes and stored in a desiccator containing silica gel until further evaluation.

2.4 Formulation Design [3,7,8]

Three formulations (F1, F2, and F3) were prepared by varying the concentrations of HPMC E15, PEG 400, propylene glycol, ethanol, and distilled water while maintaining a constant drug concentration (100 mg) in each formulation. The formulation variables were optimized to obtain patches with desirable mechanical strength, flexibility, and physicochemical characteristics.

Table 1. Composition of Promethazine Hydrochloride Transdermal Patches

Ingredients	F1	F2	F3
Promethazine Hydrochloride (mg)	100	100	100
HPMC E15 (mg)	500	300	700
PEG 400 (mL)	0.5	1	0.2
Propylene Glycol (mL)	0.5	1	0.2
Glycerine (mL)	0.3	—	—
Ethanol (mL)	5	3	2
Distilled Water (mL)	5	7	8

2.5 Evaluation of Transdermal Patches

2.5.1 Physical Appearance[3,7]

The prepared patches were visually inspected for colour, transparency, smoothness, flexibility, uniformity, presence of air bubbles, cracks, and ease of peeling from the casting surface.

2.5.2 Thickness Measurement [11]

The thickness of each transdermal patch was measured using a digital micrometer screw gauge at five different locations, including the centre and four peripheral positions. The average thickness was calculated and expressed as mean ± standard deviation (SD).

2.5.3 Weight Variation [11]

Ten patches of equal dimensions were cut from different regions of the film and individually weighed using an analytical balance. The mean weight, standard deviation, and percentage relative standard deviation (%RSD) were calculated to assess weight uniformity.

2.5.4 Drug Content Determination [12]

Drug content was determined using a UV–Visible spectrophotometer. A patch equivalent to the required amount of Promethazine Hydrochloride was dissolved in distilled water, filtered, appropriately diluted, and analyzed at the λmax of **249 nm**. Drug content was calculated using the standard calibration curve and expressed as percentage drug content.

2.5.5 Moisture Content [11]

The moisture content of the prepared patches was determined by the loss-on-drying method. Pre-weighed patch samples were dried in a hot air oven at **60°C** until constant weight was achieved. Moisture content was calculated using the following equation:

$$\text{Moisture Content (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

where:

- W_1 = Initial weight of the patch
- W_2 = Final dried weight of the patch

2.5.6 Surface pH [5]

The surface pH of the prepared transdermal patches was determined by moistening the patch with distilled water and placing universal pH paper on the surface for approximately 30 seconds. The colour developed was compared with the standard pH chart, and the corresponding pH value was recorded.

3. RESULTS AND DISCUSSION

Three formulations (F1–F3) of Promethazine Hydrochloride transdermal patches were prepared using the solvent casting technique by varying the concentrations of HPMC E15, PEG 400, propylene glycol, ethanol, and distilled water. Among the prepared formulations, F1 exhibited satisfactory film-forming characteristics, whereas F2 and F3 failed to produce acceptable films due to inappropriate polymer-to-plasticizer ratios. The prepared formulations were evaluated for their physicochemical characteristics, and the optimized formulation (F1) was selected based on its superior performance.

3.1 Optimization of Formulation

Three formulations were prepared to optimize the concentration of polymer and plasticizer required for obtaining a uniform and flexible transdermal patch.

Table 2. Comparative Evaluation of Formulations

Parameter	F1	F2	F3
Physical appearance	Smooth and uniform	Sticky	Brittle
Flexibility	Excellent	Poor	Poor
Peelability	Easy	Difficult	Cracked during peeling
Uniformity	Uniform	Non-uniform	Non-uniform
Overall result	Optimized	Failed	Failed

The concentration of HPMC E15 significantly influenced the quality of the prepared patches. Formulation F2 contained a lower concentration of polymer (300 mg), resulting in insufficient film formation and sticky patches due to excessive plasticizer and inadequate matrix strength. Conversely, formulation F3 containing 700 mg HPMC produced rigid and brittle films because of insufficient PEG 400 and solvent, leading to drug crystallization and film cracking. Formulation F1, containing 500 mg HPMC E15 with an appropriate concentration of PEG 400, propylene glycol, and glycerine, produced smooth, flexible, and easily peelable films, indicating an optimum polymer-to-plasticizer ratio. These findings agree with previous reports that HPMC concentration and plasticizer content critically influence the mechanical properties of matrix transdermal films.

3.2 Physical Appearance

The prepared patches were visually inspected for colour, transparency, smoothness, flexibility, and ease of peeling.

Table 5. Physical Appearance of Optimized Formulation

Parameter	**Observation**
Colour	Off-white to pale yellow
Surface	Smooth and uniform
Flexibility	Flexible
Transparency	Slightly opaque
Cracks	Absent
Drug crystals	Absent
Peelability	Easy

The optimized formulation (F1) exhibited a smooth, uniform surface without visible cracks, air bubbles, or drug crystals. The addition of PEG 400 and glycerine improved flexibility by reducing polymer rigidity, while HPMC E15 produced a continuous polymeric matrix. Uniform appearance also indicates homogeneous drug distribution

within the polymer network, which is essential for reproducible drug release.

3.3 Thickness

Thickness uniformity is an important quality parameter because it directly influences drug loading, mechanical strength, and release characteristics.

Table 3. Thickness of Optimized Patch (F1)

Patch	Mean Thickness (mm)
1	0.319 ± 0.003
2	0.316 ± 0.003
3	0.320 ± 0.002
Overall Mean	0.318 ± 0.003

The average thickness of the optimized formulation was 0.318 ± 0.003 mm, indicating excellent reproducibility of the solvent casting process. The very low standard deviation demonstrates uniform spreading of the casting solution and controlled solvent evaporation. The obtained thickness lies within the acceptable range (0.2–0.5 mm) generally reported for HPMC-based transdermal patches, suggesting suitability for controlled drug release.

3.4 Weight Variation

Uniform weight reflects consistent polymer distribution and uniform drug loading throughout the patch.

Table 4. Weight Variation of Optimized Patch

Parameter	Value
Mean weight	51.10 mg
Standard deviation	±0.24 mg
%RSD	0.47%
Acceptance	Pass

The optimized formulation exhibited a mean weight of 51.10 ± 0.24 mg with a %RSD of 0.47%**,** which is well below the acceptable pharmacopeial limit of 5%. The low variation confirms excellent uniformity during film casting and indicates reproducible manufacturing of the transdermal patches.

3.5 Drug Content

Drug content uniformity is an important indicator of formulation homogeneity.

Table 5. Drug Content of Optimized Patch

Parameter	Result
λmax	249 nm
Regression equation	A = 0.0218C + 0.0042
Correlation coefficient (R^2)	0.9992
Drug content	97.83 ± 0.36%

The optimized formulation showed a drug content of 97.83 ± 0.36%**,** demonstrating excellent uniformity of drug distribution throughout the polymer matrix. The calibration curve showed excellent linearity (R^2 = 0.9992), confirming the reliability of the UV spectrophotometric method. Drug content within the pharmacopeial acceptance range (90–110%) indicates negligible drug loss during formulation and drying.

3.6 Moisture Content

Residual moisture influences the mechanical strength and storage stability of transdermal patches.

Table 6. Moisture Content

Sample	Moisture (%)
1	1.91
2	1.87
3	1.94
Mean ± SD	1.91 ± 0.04

The optimized formulation exhibited a moisture content of **1.91 ± 0.04%**, indicating minimal residual moisture within the patch. Such low moisture content is desirable because it minimizes microbial growth, prevents hydrolytic degradation of the drug, and improves the storage stability of the formulation without making the films

brittle.

3.7 Surface pH

Surface pH is a critical parameter for minimizing skin irritation after topical application.

Table 7. Surface pH

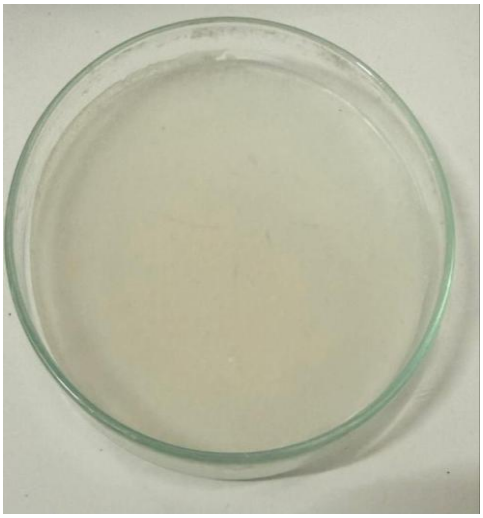
Sample	pH
1	6.2
2	6
3	6.3
Mean ± SD	6.17 ± 0.15

The optimized patch exhibited a mean surface pH of **6.17 ± 0.15**, which falls within the physiological pH range of human skin (4.5–6.5). This suggests that the prepared patch is unlikely to cause skin irritation or discomfort during prolonged application. The near-neutral pH further confirms the compatibility of the selected excipients with transdermal administration.

3.8 Overall Evaluation of Optimized Formulation

Table 8. Summary of Evaluation Parameters

Evaluation Parameter	Result	Acceptance
Physical appearance	Smooth, uniform	Pass
Thickness	0.318 ± 0.003 mm	Pass
Weight variation	0.47% RSD	Pass
Drug content	97.83 ± 0.36%	Pass
Moisture content	1.91 ± 0.04%	Pass
Surface pH	6.17 ± 0.15	Pass



Formulation F1 — Optimized transdermal patch showing smooth, uniform, off-white film after drying in petri dish

Overall, formulation **F1** demonstrated superior physicochemical characteristics compared with the other formulations. The optimized polymer concentration (500 mg HPMC E15) together with PEG 400, glycerine, and propylene glycol produced a mechanically stable, flexible, and uniform transdermal patch with satisfactory drug content and skin-compatible pH. These findings indicate that the optimized HPMC-based matrix system is a promising carrier for the transdermal delivery of Promethazine Hydrochloride. However, additional investigations, including folding endurance, tensile strength, moisture uptake, in vitro drug release, ex vivo skin permeation, stability studies, and release kinetic modeling**,** are recommended to comprehensively evaluate the formulation before clinical application.

4. CONCLUSION:

The present study successfully formulated and evaluated matrix-type transdermal patches of Promethazine Hydrochloride using the solvent casting method with Hydroxypropyl Methylcellulose (HPMC E15) as the primary film-forming polymer. Three formulations (F1–F3) were developed by varying the concentrations of polymer,

plasticizer, and permeation enhancer to optimize the physicochemical properties of the transdermal patches. Among the prepared formulations, F1 demonstrated superior film-forming characteristics, producing a smooth, flexible, uniform, and easily peelable patch without visible cracks or drug crystallization.

The optimized formulation exhibited satisfactory physicochemical properties, including uniform thickness (0.318 ± 0.003 mm), minimal weight variation (%RSD = 0.47%), high drug content (97.83 ± 0.36%), low moisture content (1.91 ± 0.04%), and a skin-compatible surface pH (6.17 ± 0.15). These results indicate excellent formulation uniformity, reproducibility, and compatibility with topical application. The study also demonstrated that the concentration of HPMC E15 and the polymer-to-plasticizer ratio are critical factors governing film integrity, flexibility, and overall performance of the transdermal patch. Lower polymer concentration resulted in sticky and non-uniform films, whereas excessive polymer concentration produced brittle and cracked patches, highlighting the importance of formulation optimization.

Overall, the optimized HPMC E15-based transdermal patch offers a promising alternative to conventional oral administration of Promethazine Hydrochloride by potentially bypassing hepatic first-pass metabolism, improving bioavailability, providing sustained drug release, and enhancing patient compliance. However, additional studies involving folding endurance, tensile strength, moisture uptake, in vitro drug release, ex vivo skin permeation using Franz diffusion cells, stability studies according to ICH guidelines, skin irritation studies, and in vivo pharmacokinetic evaluation are required to further establish the therapeutic efficacy, safety, and clinical applicability of the developed transdermal delivery system. The findings of this study provide a strong foundation for the future development of effective and patient-friendly transdermal formulations of Promethazine Hydrochloride.

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