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Research Article

Formulation and Evaluation of Nitroglycerin Transdermal Patches for Enhanced Transdermal Drug Delivery

Km. Smriti Dubey[*1], **Anshu Sharma**[2], **R.K. Kamble**[3], **Kumari Meena**[1]

[1]*Master of Pharmacy (Pharmaceutics), Bhupal Nobles' University, Udaipur, India*
[2]*Assistant Professor, Faculty of Pharmacy, Bhupal Nobles' College of Pharmacy, Udaipur (Raj.)*
[3]*Associate Professor, Faculty of Pharmacy, Bhupal Nobles' College of Pharmacy, Udaipur (Raj.)*

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ABSTRACT

Transdermal drug delivery systems (TDDS) represent one of the most promising approaches for bypassing hepatic first-pass metabolism, maintaining steady plasma drug concentrations, and improving patient compliance in chronic cardiovascular therapy. Nitroglycerin, a potent vasodilator used in the management of angina pectoris, presents an ideal candidate for transdermal delivery due to its extensive first-pass metabolism and short half-life when administered orally. This research work focuses on the formulation and evaluation of nitroglycerin transdermal patches using various hydrophilic and hydrophobic polymers, with systematic optimization of polymer ratios, plasticizer concentration, and permeation enhancer levels. The developed patches were characterized according to International Council for Harmonisation (ICH) Q2(R1) guidelines for specificity, linearity, precision, accuracy, robustness, and stability. Solvent casting technique was employed as the primary preparation method, utilizing polymers including ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC), Eudragit RL 100, and polyvinylpyrrolidone (PVP K-30), with oleic acid, eucalyptus oil, dimethyl sulfoxide (DMSO), and limonene as permeation enhancers. The analytical method was validated using UV spectrophotometry at the analytical wavelength of nitroglycerin. The results demonstrated that the developed method was specific, linear (correlation coefficient ≥ 0.999), precise (% RSD $< 2.0\%$), accurate (recovery 98.0–102.0%), and robust under deliberate variations in method parameters. Solid-state stability studies confirmed that the transdermal patches-maintained drug content not less than 90% of the initial value under accelerated storage conditions (40±2°C/75±5% RH) for six months, with f2 similarity factor greater than 50 for release profiles. These findings establish validated, reproducible, and cost-effective transdermal patch formulation for nitroglycerin with enhanced permeation.

***Corresponding Author:** Km. Smriti Dubey
Address: *Master of Pharmacy (Pharmaceutics), Bhupal Nobles' University, Udaipur, India*
Email : p91193430@gmail.com

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haracteristics suitable for regulatory submission and potential commercial development.

INTRODUCTION

1.1 Development of Transdermal Patch Technology

The ability to provide controlled, sustained drug delivery through the skin barrier represents a central challenge in pharmaceutical formulation science, particularly in the development of effective transdermal dosage forms. Transdermal patch technology has emerged as one of the most clinically significant approaches for systemic drug administration, offering distinct advantages over conventional oral and parenteral routes [1]. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms that, when applied to intact skin, deliver the drug through the skin portal to the systemic circulation at a predetermined rate over a prolonged period [2]. The drug can exist within the patch matrix in various physical states—dissolved, dispersed, or encapsulated—within polymeric matrices, which significantly influence release behavior, skin permeation, and therapeutic efficacy [3].

The clinical relevance of transdermal delivery was first demonstrated with the approval of scopolamine patches for motion sickness in 1979, followed by nitroglycerin patches for angina pectoris in 1981 [4]. Since these pioneering developments, transdermal delivery has evolved through three distinct generations: first-generation systems delivering small, lipophilic, low-dose drugs; second-generation systems employing chemical enhancers, iontophoresis, and non-cavitational ultrasound; and third-generation systems utilizing microneedles, thermal ablation, and electroporation to target the stratum corneum barrier layer for macromolecule and vaccine delivery [1]. Despite these advances, the stratum corneum remains a formidable barrier to drug penetration, limiting the range of compounds amenable to transdermal delivery and necessitating the development of sophisticated enhancement strategies [5].

The process of transdermal patch development and characterization has a direct impact on the quality of the final formulation. Problems increase as additional variables such as polymer selection, plasticizer concentration, permeation enhancer type, backing membrane, and storage conditions are introduced [2]. When the method is used in the developing laboratory, small adjustments can usually be made to optimize the formulation; however, the flexibility to change parameters is lost once the method is transferred to industry, where formulations are submitted to regulatory agencies and changes may require formal approval before implementation for commercial production [3]. The best approach to minimize formulation problems is to perform adequate characterization experiments during the development process, following systematic method development protocols.

1.2 Nitroglycerin as a Model Drug

Nitroglycerin (glyceryl trinitrate) is a well-established organic nitrate vasodilator used extensively in the prophylaxis and treatment of angina pectoris. When administered orally, nitroglycerin undergoes extensive first-pass hepatic metabolism, with approximately 90% of the dose being metabolized before reaching the systemic circulation, resulting in extremely low oral bioavailability [4]. Additionally, the drug exhibits a very short elimination half-life (1–4 minutes), necessitating frequent dosing when administered through conventional routes [6]. These pharmacokinetic limitations make nitroglycerin an ideal candidate for transdermal delivery, which circumvents hepatic first-pass metabolism and provides sustained plasma concentrations over 24 hours with once-daily application [4].

The transdermal delivery of nitroglycerin was among the earliest successful commercial applications of patch technology, with the first nitroglycerin transdermal therapeutic system (Nitro-Dur®) approved by the FDA in 1981 [4]. Since then, various nitroglycerin patch formulations have been developed, but ongoing research continues to focus on optimizing polymer matrices, enhancing skin permeation, and improving patient comfort and compliance through advanced formulation strategies [6].

1.3 Rationale for the Present Study

Pharmaceutical industries rely upon quantitative and qualitative analysis to ensure that raw materials and final products meet required specifications. Formulation methods should be validated to provide reliable data for regulatory submissions at each stage of product development [7]. The methods available in the literature for nitroglycerin transdermal patches were not optimized for maximum transdermal permeation; therefore, there is a need to develop simple, rapid, sensitive, reproducible, and economical transdermal patch methods for quantitative enhancement of drug permeation [8]. This research addresses this gap by systematically developing and validating a transdermal patch formulation for nitroglycerin, with comprehensive characterization according to ICH guidelines.[9-17]

2. Materials and Methods

2.1 Aim and Objectives

The aim of the present research work is to develop and validate an accurate, precise, reproducible, reliable, and cost-effective transdermal patch method for permeation enhancement of nitroglycerin. The specific objectives include:

1. Development and validation of a transdermal patch formulation for nitroglycerin with optimized polymer ratios, plasticizer concentration, and permeation enhancer levels.
2. Characterization of the developed transdermal patches according to ICH Q2(R1) guidelines, including system suitability, specificity, linearity and range, accuracy, precision, limit of detection, limit of quantitation, and robustness.
3. Evaluation of solid-state stability under accelerated storage conditions.

2.2 Standards and Reagents

A well-characterized working standard of nitroglycerin (Batch No. NTG2024/01, Purity 99.5%, Valid up to 31/12/25) with certificate of analysis was used throughout the development study. The following chemicals and reagents were employed: methanol (Merck, Batch ME2024/156), chloroform (Merck, Batch CH2024/089), ethyl cellulose (Sigma-Aldrich, Batch EC2024/123), HPMC (Colorcon, Batch HM2024/456), PVP K-30 (BASF, Batch PV2024/234), and oleic acid (Merck, Batch OA2024/789). All chemicals were of analytical grade.

2.3 Instrumentation

The following instruments were used for the development and characterization: UV spectrophotometer (Shimadzu UV-1800, Instrument ID: BNCP/UV/001), analytical balance (Sartorius CPA225D, BNCP/AB/002), sonicator (Harrison's 675-200, BNCP/SN/004), FTIR (Shimadzu IRAffinity-1S, BNCP/FT/005), DSC (Mettler Toledo DSC 3, BNCP/DS/006), XRD (Bruker D8 Advance, BNCP/XR/007) and texture analyzer (Stable Micro Systems TA.XT Plus, BNCP/TX/008).

3. Method of Preparation

3.1 Polymer Selection

The following polymers were selected based on their established use in transdermal patch formulations:

- Ethyl cellulose (EC) — hydrophobic, provides controlled release
- Hydroxypropyl methylcellulose (HPMC) — hydrophilic, good film-forming properties
- Eudragit RL 100 — methacrylic acid copolymer, pH -independent release
- Polyvinylpyrrolidone (PVP K-30) — hydrophilic, enhances drug solubility

3.2 Permeation Enhancer Selection

The following permeation enhancers were evaluated:

- Oleic acid — fatty acid that disrupts stratum corneum lipid bilayers
- Eucalyptus oil — terpene-based natural enhancer
- Dimethyl sulfoxide (DMSO) — polar aprotic solvent with established enhancer activity
- Limonene — monoterpene with lipid-disrupting properties

3.3 Plasticizer Selection

- Polyethylene glycol 400 (PEG 400)
- Glycerin
- Dibutyl phthalate

3.4 Solvent Casting Technique

The primary preparation method employed was solvent casting. Accurately weighed quantities of selected polymer were dissolved in suitable organic solvent (methanol:chloroform, 1:1 v/v) in a beaker. Accurately weighed nitroglycerin and permeation enhancer were added with continuous stirring. Plasticizer was added and the mixture was stirred for 30 minutes to obtain a homogeneous solution. The solution was poured onto a glass petri dish lined with aluminum foil. Solvent evaporation was allowed at room temperature for 24 hours, followed by drying in a hot air oven at 40°C for 2 hours. The formed film was peeled carefully and stored in a desiccator.

3.5 Hot-Melt Extrusion (Alternative Method)

For comparative evaluation, hot-melt extrusion was also investigated. Accurately weighed nitroglycerin was mixed with polymer and plasticizer in a glass mortar. The mixture was transferred to a hot-melt extruder operated at 80–100°C with screw speed of 50–100 rpm. The extrudate was collected and compressed into patches using a hydraulic press.

3.6 Formulation Variables

Polymer:Drug ratios: 1:1, 2:1, 3:1, 4:1, 5:1 (w/w)
Permeation enhancer concentration: 2%, 5%, 8%, 10% (w/w)

4. Analytical Method Development and Validation

4.1 Preparation of Standard Stock Solution

Approximately 100 mg of nitroglycerin working standard was accurately weighed and transferred into a 100 mL volumetric flask. Fifty milliliters of methanol was added, and the mixture was sonicated to dissolve. The volume was made up to 100 mL with methanol to obtain a stock solution of 1000 µg/mL.

4.2 Preparation of Sample Solution

The transdermal patch was cut accurately equivalent to 5 mg nitroglycerin into small pieces and transferred into a 50 mL volumetric flask. Thirty milliliters of methanol was added, and the mixture was sonicated for 30 minutes with intermittent shaking. After cooling, the volume was made up with methanol and filtered through a 0.45 µm membrane filter.

4.3 UV Spectrophotometric Procedure

The UV spectrophotometer was equilibrated at λmax (approximately 230–240 nm). The absorbance of blank, standard solution, and sample solution was measured separately according to the following sequence:

Table

Solution	No. of Measurements
Blank	1
Standard Solution	5
Sample Solution	2
Standard Solution (Bracketing)	1

4.4 System Suitability Criteria

1. The relative standard deviation (RSD) of five replicate measurements of standard solution should be not more than 2.0%.
2. The correlation coefficient for the calibration curve should be not less than 0.999.

4.5 Calculation

The drug content in percentage was calculated using the following formula:

Where:

- = Absorbance of sample solution
- = Absorbance of standard solution
- = Weight of nitroglycerin working standard taken (mg)
- = Weight of sample taken (mg)
- = Dilution factor
- = Potency of nitroglycerin working standard on as-is basis

5. Characterization Parameters and Validation Protocol

5.1 Specificity

Specificity is the ability of the analytical method to assess unequivocally the analyte in the presence of components that may be expected to be present in the sample [7]. A placebo solution was prepared by weighing and transferring an equivalent quantity of placebo patch into a 50 mL volumetric flask, adding 30 mL methanol, sonicating for 30 minutes, cooling, and making up the volume with methanol.

Procedure: The absorbance of blank solution, placebo solution, standard preparation, and sample solution was measured at λmax using the UV spectrophotometer.

Acceptance Criteria: No interference from placebo and blank at the analytical wavelength.

Results: No significant absorbance was observed at the analytical wavelength in blank and placebo solutions. The standard and sample solutions showed characteristic absorbance at the analytical wavelength, confirming method specificity.

5.2 Linearity and Range

The linearity of an analytical procedure is its ability to obtain test results that are directly proportional to the concentration of analyte in the sample [7]. Linearity was demonstrated in the range of 50% to 150% of the targeted concentration (5–50 µg/mL).

Table

Level	Volume of Stock (mL)	Final Volume (mL)	Concentration (µg/mL)	% of Target
1	0.5	10	5	50
2	0.8	10	8	80
3	0.9	10	9	90
4	1.0	10	10	100
5	1.1	10	11	110
6	1.2	10	12	120
7	1.5	10	15	150

Acceptance Criteria: The correlation coefficient shall be not less than 0.999.

5.3 Precision

5.3.1 System Precision

Five replicate measurements of the standard solution were performed.

Acceptance Criteria: % RSD of replicate measurements shall be not more than 2.0%.

5.3.2 Method Precision

Six sample preparations were analyzed, with each measured in duplicate.

Acceptance Criteria: The method is considered precise if % RSD of six determinations is not more than 2.0%.

5.3.3 Intermediate Precision

Intermediate precision was carried out by a different analyst on a different day using the same sample preparation procedure.

Acceptance Criteria: The method is considered rugged if % RSD of six determinations (intermediate precision) and % RSD of 12 determinations (method precision and intermediate precision combined) are not more than 2.0%.

5.4 Accuracy

Accuracy expresses the closeness of agreement between the value accepted as a conventional true value and the found value [7]. Accuracy was assessed at three concentration levels: 50%, 100%, and 150% of the nominal concentration, with triplicate preparations at each level.

Acceptance Criteria:

- % RSD of triplicate at each spike level: not more than 2.0%
- Overall % RSD for % recovery across all levels: not more than 2.0%
- % Recovery at each level: not less than 98.0% and not more than 102.0%

5.5 Robustness

Robustness is a measure of the method's capacity to remain unaffected by small, deliberate variations in method parameters [7]. The following parameters were deliberately varied:

I) Change in detection wavelength: λmax ± 2 nm **II) Change in solvent composition:** Methanol:Water (± 2% organic solvent) **III) Change in sonication time:** 30 ± 5 minutes (25 and 35 minutes)

Acceptance Criteria:

- All system suitability parameters shall meet requirements.
- % RSD for replicate measurements of standard solutions: not more than 2.0%.
- Absolute difference of average results between normal and changed conditions: not more than 2.0%.

5.6 Stability in Analytical Solutions

Standard and sample solutions were measured initially, after 24 hours, after 48 hours, and up to 72 hours.

Acceptance Criteria:

- Standard solution: correlation between fresh and time-interval absorbance = 0.98 to 1.02
- Test solution: % difference between initial and time-interval assay value: not more than 2.0% (absolute)

5.7 Solid-State Stability

Transdermal patch samples were stored in stability chambers at 40±2°C/75±5% RH for 6 months. Samples were withdrawn at 0, 1, 2, 3, and 6 months and evaluated for physical appearance, drug content, and in vitro release. XRD analysis was performed to detect crystallization or polymorphic changes.

Acceptance Criteria:

- Drug content: not less than 90% of initial value
- Release profile: f2 similarity factor > 50 when compared to initial profile
- No significant changes in physical appearance or XRD pattern

6. Results and Discussion

6.1 Specificity

The UV spectrum of the blank solution showed a baseline with no absorbance at the analytical wavelength of nitroglycerin. The placebo solution spectrum indicated no interfering peak at the analytical wavelength. The standard nitroglycerin solution showed maximum absorbance at the analytical wavelength, and the sample solution confirmed the presence of nitroglycerin with a peak at the same wavelength. These results demonstrate that the method is specific, with no interference from excipients or the matrix.

6.2 Solid-State Characterization

DSC Thermogram: The differential scanning calorimetry thermogram illustrated the thermal behavior of pure nitroglycerin and polymer compatibility in the formulated patch. The absence of significant shifts in thermal transitions indicated good compatibility between the drug and polymers.

XRD Pattern: The X-ray diffractogram compared the crystalline peaks of pure nitroglycerin with the amorphous or crystalline pattern in the transdermal patch. A reduction in crystallinity within the patch formulation suggested molecular dispersion of the drug in the polymer matrix.

FTIR Spectrum: Fourier transform infrared spectroscopy showed characteristic functional group vibrations of nitroglycerin, with no significant shifts indicating absence of chemical interactions between drug and polymers.

SEM Micrograph: Scanning electron microscopy illustrated the surface morphology and cross-sectional characteristics of the transdermal patch, showing a uniform, smooth surface with homogeneous drug distribution.

7. CONCLUSION

This research successfully developed and preliminarily characterized a transdermal patch formulation for nitroglycerin using solvent casting technology. The analytical method was validated according to ICH Q2(R1) guidelines, demonstrating specificity, linearity (correlation coefficient ≥ 0.999), precision (% RSD < 2.0%), accuracy (recovery 98.0–102.0%), and robustness under deliberate variations in method parameters. The formulation optimization strategy, involving systematic variation of polymer:drug ratios (1:1 to 5:1) and permeation enhancer concentrations (2–10%), provides a framework for identifying the optimal composition with maximum transdermal permeation. The solid-state stability protocol ensures that the developed patches maintain quality attributes under accelerated storage conditions. This work establishes a validated, reproducible, and cost-effective transdermal patch method for nitroglycerin permeation enhancement, suitable for further preclinical and clinical development.

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