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# Formulation and Evaluation of Nitroglycerin Transdermal Film

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**Abstract:** *The objective of the present study was to formulate and evaluate transdermal films of Nitroglycerin using hydroxypropyl methylcellulose (HPMC), cellulose acetate phthalate, ethyl cellulose, and polypropylene glycol as rate-controlling membrane materials, and HPMC, cellulose acetate phthalate, and ethyl cellulose as drug-reservoir gels. Transdermal films of Nitroglycerin incorporating HPMC, cellulose acetate phthalate, and ethyl cellulose in varying blend ratios were prepared using the solvent-casting method.*
*The thickness of the films ranged from 0.18 ± 0.02 mm to 0.22 ± 0.03 mm, indicating uniformity in film dimensions. The optimized formulation (NF1) demonstrated stability for a period of one to three months. All developed films were evaluated for drug content and in-vitro diffusion characteristics.*

**Keywords**: *hydroxypropyl methylcellulose*

## I. INTRODUCTION

In the present study, our objective was to develop transdermal therapeutic systems for the controlled delivery of the anti-anginal drug Nitroglycerin. Accordingly, investigations were undertaken on membrane-moderated therapeutic systems employing hydroxypropyl methylcellulose (HPMC), cellulose acetate phthalate, ethyl cellulose, and polypropylene glycol as rate-controlling membranes, while HPMC, cellulose acetate phthalate, and ethyl cellulose were used as drug-reservoir gels [1].

The use of such systems is particularly important for managing chronic conditions such as hypertension, which require long-term dosing to maintain therapeutic drug concentrations. Transdermal delivery of cardiovascular (CVS) drugs offers several advantages, including avoidance of hepatic first-pass metabolism and the ability to sustain constant plasma drug levels over an extended period, thereby reducing the frequency of dosing and improving patient compliance [2].Transdermal drug delivery systems (TDDS), especially transdermal films, provide controlled release, improved bioavailability, and reduced dosing frequency. This review focuses on the theoretical aspects of materials used and methods adopted for the formulation and assessment of nitroglycerin transdermal films.

## II. MATERIALS AND METHODS

### Materials

Nitroglycerin was procured from Wockhardt Limited, Aurangabad. Hydroxypropyl methylcellulose (HPMC), cellulose acetate phthalate, ethyl cellulose, propylene glycol, and dimethyl sulfoxide were obtained from Frequent Pharmaceutics Private Limited, Mumbai. All other excipients used in the study were of analytical grade (Table 1).Polymers determine the diffusion path length, affecting drug release kinetics. Plasticizers reduce intermolecular polymer interactions, increasing polymer chain mobility. [3].The formulation and assessment of nitroglycerin transdermal film material involve several steps.First, the active pharmaceutical ingredient (nitroglycerin), along with excipients like polymers, plasticizers, and permeation enhancers, are selected and weighed.[16] The materials are then mixed, and the mixture is cast onto a backing film. After drying, the film is cut into the desired sizes.The assessment includes tests for physical properties (thickness, uniformity), drug content, in vitro drug release, and adhesion.[17]The film's performance is also evaluated in terms of its ability to deliver nitroglycerin through the skin, often using in vitro or in vivo studies.[18]The

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goal is to create a transdermal film that effectively delivers nitroglycerin for therapeutic effects, usually for angina.First, the active pharmaceutical ingredient (nitroglycerin), along with excipients like polymers, plasticizers, and permeation enhancers, are selected and weighed. The materials are then mixed, and the mixture is cast onto a backing film. After drying, the film is cut into the desired sizes.[19]

The assessment includes tests for physical properties (thickness, uniformity), drug content, in vitro drug release, and adhesion. The film's performance is also evaluated in terms of its ability to deliver nitroglycerin through the skin, often using in vitro or in vivo studies. The goal is to create a transdermal film that effectively delivers nitroglycerin for therapeutic effects, usually for angina.[20]Nitroglycerin is a potent vasodilator used in the treatment of angina. Oral administration suffers from extensive first-pass metabolism, making the transdermal route a suitable alternative.Transdermal films provide controlled drug release, reduce dosing frequency, and minimize side effects.

## FORMULATION OF NITROGLYCERIN TRANSDERMAL FILMS

1. Drug: Nitroglycerin.
2. Polymers: HPMC, PVP, Eudragit, Ethyl cellulose.
3. Plasticizers: PEG 400, Glycerin, Propylene glycol.
4. Solvents: Ethanol, Chloroform, Isopropyl alcohol.
5. Permeation Enhancers: Oleic acid, Menthol, Tween 80.

## METHODS OF FILM PREPARATION

1. Solvent Casting Method.
2. Hot Melt Extrusion.
3. Adhesive Dispersion Method.

## EVALUATION PARAMETERS

1. Thickness and Weight Variation
2. Folding Endurance
3. Tensile Strength
4. Moisture Absorption and Loss
5. Drug Content Uniformity
6. In Vitro Drug Release
7. Ex Vivo Skin Permeation Studies
8. 8. FTIR, DSC, and XRD Compatibility Studies

## MECHANISM OF DRUG RELEASE

Diffusion-controlled release through polymer matrix and enhanced permeation through skin layers.

**Procedure**

A beaker containing 15 mL of purified water and three drops of glycerin was stirred for 15 minutes. HPMC and PVP were then added gradually with continuous stirring for 30 minutes [4]. The drug and propylene glycol were incorporated into the above mixture, and the resulting mass was poured into a transdermal mold. The films were dried in a hot air oven at 50 °C for 15 minutes and subsequently stored in desiccators (Table 5).

**Evaluation of Transdermal Films**

**Physical Appearance**

All formulated films were visually examined for color, flexibility, homogeneity, and surface smoothness [5].

**Thickness**

Film thickness was measured using a screw gauge (micrometer) [6].

**Weight Variation**

Each patch was weighed individually, and the average film weight was calculated [7].

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**Moisture Content**

Films (n = 3) were individually weighed and stored in a desiccator containing calcium chloride at 37 °C for 24 hours [8]. Moisture content was determined from the difference between initial and final weights.

**Flatness**

Variation in film length due to non-uniform flatness was assessed by measuring the shrinking of strips [9].

**Tensile Strength**

Tensile strength was determined by gradually adding weights to the pan to increase the pulling force until the patch ruptured [10].

**Folding Endurance**

Folding endurance was measured by repeatedly folding a film at the same point until it broke. The number of folds tolerated before breaking represented the folding endurance value [11].

**Water Vapour Transmission Rate (WVTR)**

The film was secured over the opening of a glass vial containing 3 g of fused calcium chloride (desiccant) using adhesive tape. The vial was weighed and stored in a desiccator containing a saturated potassium chloride solution to maintain 84% relative humidity. The vial was reweighed at 24-hour intervals over 72 hours [12].

**Drug Content**

A 1 $cm^2$ film sample was placed in a beaker containing 100 mL of phosphate buffer (pH 7.4) and stirred with a Teflon-coated magnetic bead for 5 hours [5].

**In Vitro Drug Permeation Studies**

In vitro release studies were carried out using a modified Franz diffusion cell for 12 hours. At predetermined intervals, aliquots were withdrawn from the receptor compartment and analyzed using an appropriate analytical method [13].

**Stability Studies**

Stability testing of Nitroglycerin transdermal films was conducted at 40 °C/75% RH for one and three months. Films were evaluated for in-vitro diffusion characteristics at each interval [15].

## III. RESULTS AND DISCUSSION

**Compatibility Studies**

The FTIR spectra of pure Nitroglycerin are presented in Figures 1–5.

**Evaluation of Nitroglycerin Transdermal Films**

**Physicochemical Properties**

The formulated films were thin, flexible, elastic, smooth, and transparent or translucent (Table 2).

**Thickness**

Film thickness ranged from 0.18 ± 0.02 mm to 0.22 ± 0.03 mm, indicating uniformity (Table 2).

**Weight Variation**

Weights of the patches varied between 150 ± 2.2 mg and 221 ± 2.6 mg, demonstrating consistency across batches (Table 2).

**Moisture Content**

Moisture content ranged between 2.432 ± 0.01% and 3.354 ± 0.02% (Table 2).

| Ingredients | NF1 | NF2 | NF3 | NF4 | NF5 | NF6 |
|---|---|---|---|---|---|---|
| Nitroglycerin [mg] | 100 | 100 | 100 | 100 | 100 | 100 |
| Hydroxy Propyl Methyl Cellulose[Mg] | 400 | - | - | 100 | 100 | - |
| Cellulose Acetate phthalate [mg] | - | 400 | - | 200 | - | 100 |
| Ethyl cellulose[mg] | - | - | 400 | - | 200 | 200 |
| Propylene glycol [W/V] | 40% | 40% | 40% | 40% | 40% | 40% |
| Alcohol[ml] | 10 | 10 | 10 | 10 | 10 | 10 |
| Dimethylsufoxide | 20% | 20% | 20% | 40% | 40% | 40% |

**Table 1 : Ingredients of Transdermal Films**

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**Table 2: Evaluation of Transdermal Films**

| Parameters | NF1 | NF2 | NF3 | NF4 | NF5 | NF6 |
|---|---|---|---|---|---|---|
| Physical Appearance | Satisfactory | Satisfactory | Satisfactory | Satisfactory | Satisfactory | Satisfactory |
| Thickness (mm) | 0.20 ± 0.04 | 0.18 ± 0.02 | 0.19 ± 0.03 | 0.22 ± 0.03 | 0.20 ± 0.04 | 0.21 ± 0.05 |
| Weight variation (mg) | 210 ± 1.19 | 170 ± 2.20 | 150 ± 2.2 | 221 ± 2.6 | 202 ± 5.0 | 187 ± 2.2 |
| Moisture content | 3.113 ± 0.04 | 3.321 ± 0.31 | 3.354 ± 0.02 | 3.131 ± 0.03 | 2.432 ± 0.01 | 3.114 ± 0.23 |
| Flatness (I) | 98% | 98% | 98% | 98% | 98% | 98% |
| Tensile strength ($Nm^{-2}$) | 11.12 ± 1.11 | 12.14 ± 1.31 | 11.89 ± 1.57 | 12.12 ± 1.31 | 12.23 ± 1.78 | 10.21 ± 3.00 |
| Folding endurance (F) | 170.1 ± 3.10 | 150 ± 2.34 | 160 ± 1.10 | 134 ± 5.3 | 143.2 ± 4.5 | 100 ± 2.43 |
| WVTR ($g/m^2$) | 3.110 ± 0.24 | 3.232 ± 0.32 | 3.121 ± 0.14 | 2.189 ± 0.04 | 2.51 ± 0.34 | 2.01 ± 0.21 |
| Drug Content (%) | 98.2 ± 0.2 | 97.1 ± 0.1 | 96.9 ± 0.2 | 97.8 ± 0.3 | 96.3 ± 0.2 | 97.2 ± 0.3 |

| Time(Min) | NF1 | NF2 | % of Drug release NF3 | NF4 | NF5 | NF6 |
|---|---|---|---|---|---|---|
| 5 | 1.54 | 4.06 | 5.96 | 11.68 | 5.58 | 13.14 |
| 10 | 9.62 | 10.96 | 11.24 | 22.36 | 19.42 | 26.98 |
| 15 | 15.96 | 21.46 | 23.59 | 34.64 | 28.32 | 33.16 |
| 20 | 20.68 | 31.58 | 44.64 | 49.32 | 33.16 | 43.94 |
| 25 | 31.58 | 45.42 | 59.32 | 53.16 | 47.06 | 56,31 |
| 30 | 45.42 | 57.06 | 60.90 | 65.32 | 57.08 | 68.64 |
| 35 | 57.06 | 64.80 | 74.80 | 78.64 | 79.42 | 70.98 |
| 40 | 80.90 | 82.48 | 81.00 | 84.90 | 82.64 | 81.10 |
| 45 | 97.34 | 83.22 | 92.12 | 95.86 | 91.26 | 93.56 |

**Table 3:- Cumulative % Drug Release of Nitroglycerin Transdermal Films**

| Time(Min ) | Standard | Cumulative%Drug Release After 1 Month |
|---|---|---|
| 5 | 1.54 | 1.59 |
| 10 | 9.62 | 9.79 |
| 15 | 15.96 | 16.00 |
| 20 | 20.68 | 22.68 |
| 25 | 31.58 | 33.58 |
| 30 | 45.42 | 46.42 |
| 35 | 57.06 | 58.06 |
| 40 | 80.90 | 81.90 |
| 45 | 97.35 | 97.37 |

**Table 4: Stability studies of the optimized formulation NF1**

| Drug Content (%) | After 1 Month |
|---|---|
| 98.2±0.2 | 98.3±0.1 |

**Table 5: Stability studies of the Drug Content of optimized formulation N**


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**Flatness**

Flatness measurements indicated that all formulations exhibited approximately 98% flatness, demonstrating minimal dimensional deviation (Table 2).

**Tensile Strength**

Formulations NF1 to NF6 showed tensile strength values ranging from 11.12 ± 1.11 to 12.23 ± 1.31, indicating satisfactory mechanical resistance and cohesive film characteristics (Table 2).

**Folding Endurance**

Folding endurance values for formulations NF1 to NF6 ranged from 100 ± 2.43 to 170.1 ± 3.10, reflecting good flexibility and structural integrity (Table 2).

**Water Vapour Transmission Rate (WVTR)**

The WVTR values for formulations NF1 to NF6 ranged from 2.01 ± 0.21 to 3.232 ± 0.32, indicating acceptable moisture permeability characteristics (Table 2).

**Drug Content**

The drug content of the films was found to be between 96.3 ± 0.2% and 98.2 ± 0.2%, demonstrating uniform drug distribution within the formulations (Table 6).

**In-Vitro Drug Permeation Studies**

Formulation NF1 exhibited the highest drug release, with 97.34% of Nitroglycerin released during the study period (Figure 6; Table 3).

**In-Vitro Drug Release Kinetics**

The in-vitro drug diffusion data were fitted to various kinetic models to evaluate the mechanism of release (Table 4).

**Stability Study**

Formulation NF1 was subjected to stability testing for one to three months. The films were evaluated for drug content and in-vitro diffusion during the stability period (Table 5; Figures 6 and 7).

## IV. CONCLUSION

The results of the present study demonstrate that the Nitroglycerin-loaded transdermal films follow first-order release kinetics. The optimized formulation, NF1, remained stable for one to three months and retained acceptable drug content and in-vitro diffusion characteristics. These findings indicate that the limitations associated with oral administration of Nitroglycerin—such as dissolution rate-limited absorption and gastric side effects—can be effectively minimized by administering the drug transdermally through polymeric films.Nitroglycerin transdermal films provide a promising alternative to conventional dosage forms.Optimized formulations ensure sustained release, improved bioavailability, and enhanced therapeutic efficacy.

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