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Transdermal Drug Delivery of Nitroglycerin Using Eucalyptus Oil in Management of Angina Pectoris

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***Abstract*: *Objective:* The goal of the current study was to create a transdermal patch containing Nitroglycerin and Eucalyptus Oil for the treatment of Angina Pectoris. These studies revealed a synergistic vasodilator effect between the medication and eucalyptus oil. *Methods:* Using HPMC K4M and ethyl cellulose as hydrophilic and hydrophobic polymers with eucalyptus oil in various ratios, Transdermal Patches containing Nitroglycerin were produced. The thickness, folding durability, weight uniformity, content uniformity, swelling index, % moisture content, moisture absorption, surface pH, and in vitro release experiments were just a few of the assessment criteria that were used to all of the patches. *Results:* Transdermal patch formulation TD3 demonstrated prolonged drug release (89% for 24 hours) in in vitro release experiments.**

***Keywords*: transdermal drug delivery, nitroglycerin, eucalyptus oil as permeation enhancer, synergistic.**

1. Introduction

Transdermal patches are used to treat a variety of disorders. Transdermal drug delivery system (TDDS) is a generally established method of medication delivery. Transdermal administration promotes patient compliance and avoids first-pass metabolism, respectively, leading to over-injectable and oral methods. They can even lessen the risk of systemic side effects by minimizing plasma concentrations when compared to oral therapy, provide a sustained release of drug at the site of application, and have low absorption. They can also prevent drug-related gastrointestinal issues, pH and emptying rate effects, and hepatic first-pass metabolism, increasing the bioavailability of the drug. The transdermal medication administration technique seeks to minimize drug retention and metabolism in the skin at the expense of increasing skin flux into systemic circulation [1].

In 1981, the FDA approved the first transdermal patch created by the California-based Alza Corp. to cure motion sickness using the medication scopolamine (Transderm-Scop). This was followed by Transdermal-nitro to treat angina pectoris.

Vasodilator nitroglycerin (1,2,3 propanetrial trinitrate, often known as TNG) has long been used to treat angina pectoris. It comes in the forms of chewing capsules, sublingual pills, and mouth spray for the treatment of angina. Acute myocardial infarction can be treated using injection solutions. Through the local generation of nitrous oxide (NO), it lowers the smooth muscle tone of blood vessels. When administered orally, due to its lipophilic nature, it is quickly absorbed and widely dispersed before being eliminated by the kidneys [2].

Eucalyptus oil contains 1,8-cineole, a monoterpene cyclic ether that can increase the penetration of both lipophilic and hydrophilic substances, eucalyptus oil is a potent skin penetration enhancer. The astringent substances known as tannins are present in eucalyptus oil. Although it shouldn't be used on the skin by itself, it can help clean the skin and hair and lessen excess oiliness when used in cosmetics. Because it contains 1,8-cineole, a monoterpene cyclic ether that can increase the penetration of both lipophilic and hydrophilic substances, eucalyptus oil is a potent skin penetration enhancer. Because it is a vasodilator, it immediately affects the artery walls and prevents them from tightening or narrowing. Eucalyptus oil has been shown to be useful in lowering inflammation, edoema, and pain. It assists in lowering the inflammation in the upper chest area [3].

Table 1
Characteristics of three types of possible administration routs for NG [2]

	Sublingual tables	Infusion	Transdermal patch
Therapeutic effect(min)	1-3	1-2	30-60
Duration of action(hr)	0.5-1	0.05-0.1	8-10
Bioavailability (%)	38.5	<100	75
Peak plasma concentration(mg/ml)	3	-	<0.5

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2. Material and Methods

A. Materials

- Nitroglycerine (Yarrow Chem Product, West Mumbai)
- Eucalyptus oil BP (Waghdole Aushdalaya, Satara)
- Hydroxypropyl methylcellulose (HPMC)
- Polyethylene glycol

Table 2
Formula for preparation of Nitroglycerine transdermal patches [5]

Ingredients	TD1	TD2	TD3
Nitroglycerine (Mg)	4	4	4
Polyethylene glycol (ml)	0.3	0.3	0.3
HPMC (mg) [%]	8.4 [100]	-	-
HPMC K4M	-	7.5 [90]	-
HPMC K4M+ethyl cellulose	-	-	6.7 [80]
Eucalyptus oil (ml)	0.2	0.2	0.2

B. Preparation of Nitroglycerin Transdermal Patches [3],[4],[1]

1. Nitroglycerine transdermal patch prepared according to formulation table by using solvent casting method.
2. Nitroglycerine was added into mixture of varying ratio of oil and plasticizer.
3. The above mixture was added to an aqueous mixture of polymer and mixed intimately by stirring for 5 min.
4. The mixture was then casted on a petri-dish and air dried for 48 hours.
5. There after air dried patch were removed from petri-dish.
6. Cut into a 2×1cm2 patch size.
7. Stored in between foil to retain their flatness, in airtight container.

C. Evaluation of Transdermal Patches

1) Thickness

A micrometre screw gauge was used to measure the thickness of numerous batches of patches at various locations on their surface, and the average thickness was noted [4].

2) Folding endurance

A certain portion of the strip (2x2 cm) was consistently cut and folded repeatedly until it broke. The number of times the film was folded at the same spot before it broke or developed obvious cracks defined the value of the folding endurance [4].

3) Percentage moisture content

After being individually weighed and kept at room temperature for 24 hours in a desiccator containing fused calcium chloride, the prepared transdermal films were reweighed and the percentage moisture content was calculated using the following formula.

Percentage Moisture Content = Initial weight − Final weight/ Final weight x100 [4]

4) Percentage moisture uptake

The produced transdermal films were individually weighed and stored for 24 hours at room temperature in a desiccator containing a fused saturated potassium chloride solution to maintain 84% RH. The films were reweighed after 24 hours, and the % moisture uptake was determined using the procedure below.

Percentage Moisture Uptake=Final weight Initial weight / Initial weight x 100 [4]

5) Drug content

A patch was taken from each batch and put in a 50 ml beaker with 20 ml of phosphate buffer solution (pH 6.4), which was then agitated sporadically until the patch was completely dissolved. This solution was further diluted by one millilitre in nine millilitres of pH 6.4 phosphate buffer. After filtering the solution, a UV/Visible spectrophotometer was used to measure the nitroglycerine concentration spectrophotometrically at a maximum of 273 nm.

6) Swelling study

The transdermal patches were individually weighed (W1) and incubated at 370.5 °C in agar gel (2%) plates as part of a swelling investigation. Every 15 minutes for up to an hour, the patches were taken out of the petri dish at regular intervals, and any surplus water was carefully wiped away with filter paper. The enlarged patches were reweighed (W2), and the formula was used to compute the swelling index [4].

Index of swelling = W2 W1/ W1 × 100

D. Compatibility Studies

1) Fourier transforms infra- red (FTIR) spectroscopy

A patch was crushed in tiny pieces and about 5.0 mg of the particles was blended with dried potassium bromide (KBr) powder to 200 mg, and compressed into a tablet using a hydraulic press. The compressed tablet was then scanned at an IR range of 4000 - 750 cm^{-1}.

2) In Vitro drug release studies

For the in vitro drug release tests, a Franz diffusion cell with a receptor compartment capacity of 60 ml was used. A membrane made of cellulose acetate from the prepared transdermal patches was used to determine the drug. The dispersion cell's benefactor and receptor compartments were isolated by a 0.45 pore size cellulose acetic acid derivation layer. After mounting the prepared transdermal patch on the cellulose acetate membrane, aluminum foil was used to seal it. The receptor compartment of the diffusion cell was filled with phosphate buffer 0.2 M pH 6.8. According to Simon et al., the whole thing was mounted on a hot plate magnetic stirrer. During the experiments with magnetic beads, the solution was continuously stirred at 50 rpm. in the receptor compartment, while the temperature was kept up with at 37+0.5 °C, which relates to typical human internal heat level. The examples were taken at different stretches (0,1,2,4,8,12 hours) and, spectrophotometrically investigated for drug content. Because air bubbles can easily enter the receiver compartment when samples are taken, manual sampling during the experiment requires constant careful attention. At each example evacuation, the receptor step was recharged with an equivalent volume of phosphate buffer.

Table 3
Result

Batches	Weight (g)	Thickness (mm)	Folding Endurance (n)	Moisture Content (%)	Moisture Uptake (%)	Drug content (%)
TD1	0.21±0.02	0.70±0.00	310±0.00	32±0.00	24±0.000	88±0.00
TD2	0.22±0.02	051±0.28	307±1.15	53±0.00	20±0.000	88±1.15
TD3	0.21±0.02	0.53±0.02	303±2.00	5.0±0.03	10±0.0190	98±0.00
TD4	0.21±0.02	0.70±0.02	301±40.10	10±0.02	26±0.000	99±0.00

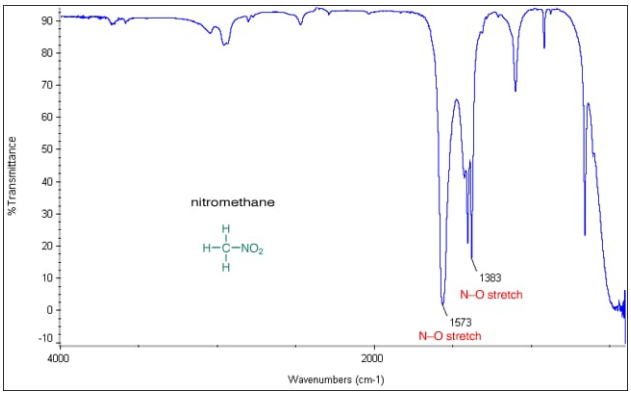

Fig. 1. IR result

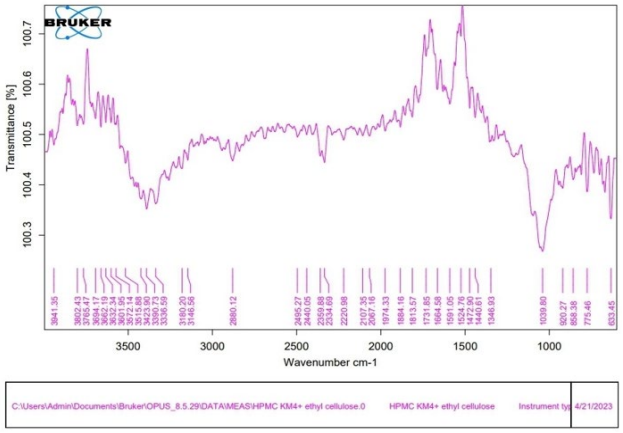

Fig. 2. FTIR spectra of Nitroglycerin with HPMC K4M and ethyl cellulose formulated transdermal patch

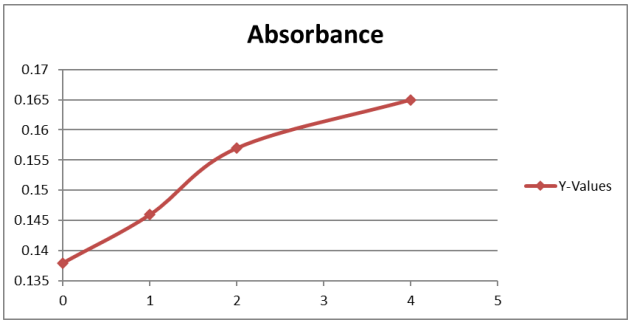

Fig. 3. In vitro drug release study

If drug have lipophilic nature, then polymer must have hydrophilic nature (opposite) nature for higher drug release through skin.

And also, polymer having lipophilic and lipophobic combination.

Hence Nitroglycerin with HPMC K4 and Ethyl cellulose gives better result than plane Nitroglycerin.

Nitroglycerin has lipophilic nature and HPMC KM4 and Ethyl cellulose have combination.

In performed batches various combination and concentration of both hydrophilic and hydrophobic polymer were used but based on drug release study of transdermal patch by using franz diffusion apparatus patch containing HPMC K4M and ethyl cellulose were selected. Transdermal patch of Nitroglycerin was prepared by solvent casting method to achieve and control release and improve bioavailability of drug.

The in vitro drug release characteristic of formulated transdermal patch is calculated by slope intercept (y=mx+c). The transdermal patch shows percentage release 89%.

3. Conclusion

Using eucalyptus oil as a permeation Enhancer, the study's goal was to create and in vitro test a transdermal Nitroglycerin patch for the treatment of angina pectoris.

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