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Research Article

Development and Evaluation of a Transdermal Patch of *Acorus calamus* for the Management of Diabetic Neuropathy

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ABSTRACT

Diabetic neuropathy is a chronic and progressive microvascular complication of diabetes mellitus, affecting up to 50% of diabetic patients. It is characterized by peripheral nerve damage resulting in sensory loss, pain, and motor deficits, severely affecting patients' quality of life. Current pharmacological therapies are often limited by systemic toxicity, poor patient compliance, and variable efficacy. In this context, transdermal drug delivery systems (TDDS) offer an attractive alternative by providing controlled drug release, improved bioavailability, and avoidance of first-pass metabolism. Acorus calamus, also known as sweet flag, is an aromatic medicinal herb traditionally used in Ayurvedic and Chinese medicine for its neuroprotective, analgesic, anti-inflammatory, and antioxidant activities. Its major bioactive constituents, particularly β-asarone and eugenol, have shown promise in modulating oxidative stress and inflammatory pathways implicated in neuropathic pain. The present study aimed to formulate and evaluate a transdermal patch of Acorus calamus extract for the effective treatment of diabetic neuropathy. The hydroalcoholic extract of Acorus calamus rhizome was prepared by maceration and standardized using phytochemical analysis and HPLC profiling. The transdermal patches were developed using the solvent casting method with polymers such as HPMC (hydroxypropyl methylcellulose) and PVP (polyvinylpyrrolidone), along with suitable plasticizers like glycerin. The formulated patches were evaluated for physicochemical parameters including thickness, weight uniformity, folding endurance, tensile strength, surface pH, drug content uniformity, and moisture content. In conclusion, the Acorus calamus-based transdermal patch represents a promising phytopharmaceutical approach for the management of diabetic neuropathy with improved patient adherence and minimal side effects.

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INTRODUCTION

Diabetic neuropathy is one of the most prevalent complications of diabetes mellitus, affecting nearly 50% of diabetic patients over time. It primarily involves progressive nerve damage due to prolonged hyperglycaemia, resulting in symptoms such as burning sensations, tingling, numbness, and chronic pain, especially in the lower limbs. Traditional pharmacological treatments, including anticonvulsants, antidepressants, and analgesics, are often associated with systemic side effects and poor patient compliance due to the need for frequent dosing. In recent years, transdermal drug delivery systems (TDDS) have emerged as a promising approach for managing neuropathic pain in diabetic patients. Transdermal patches provide a non-invasive method to deliver drugs across the skin either locally or systemically, ensuring sustained release, avoiding gastrointestinal irritation, and bypassing first-pass hepatic metabolism. Medications like **lidocaine**, **capsaicin**, and **opioids** (e.g., buprenorphine or fentanyl) have been successfully used in transdermal forms to alleviate neuropathic pain. The development and application of transdermal patches in diabetic neuropathy offer improved therapeutic outcomes, enhanced patient compliance, and reduced side effects, thereby representing a valuable advancement in pain management strategies for diabetic populations.

Diabetes Mellitus:

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. It is one of the most pressing global health challenges of the 21st century, with rising prevalence across all age groups.

Types of Diabetes Mellitus:

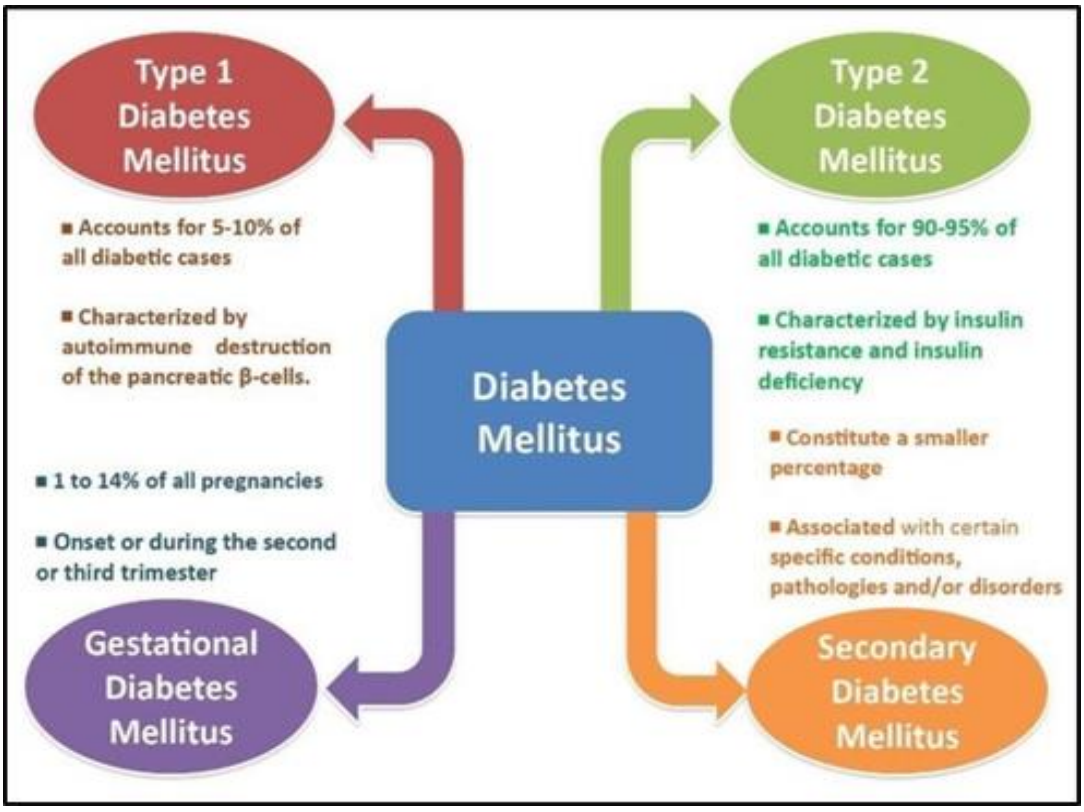


Fig - Types of Diabetes Mellitus

Diabetic Neuropathy:

Diabetic neuropathy is a type of nerve damage that occurs as a complication of both type 1 and type 2 diabetes. It is caused by prolonged exposure to high blood glucose levels, which damages nerves throughout the body, most commonly in the legs and feet. It affects up to 50% of people with diabetes during their lifetime. [5]

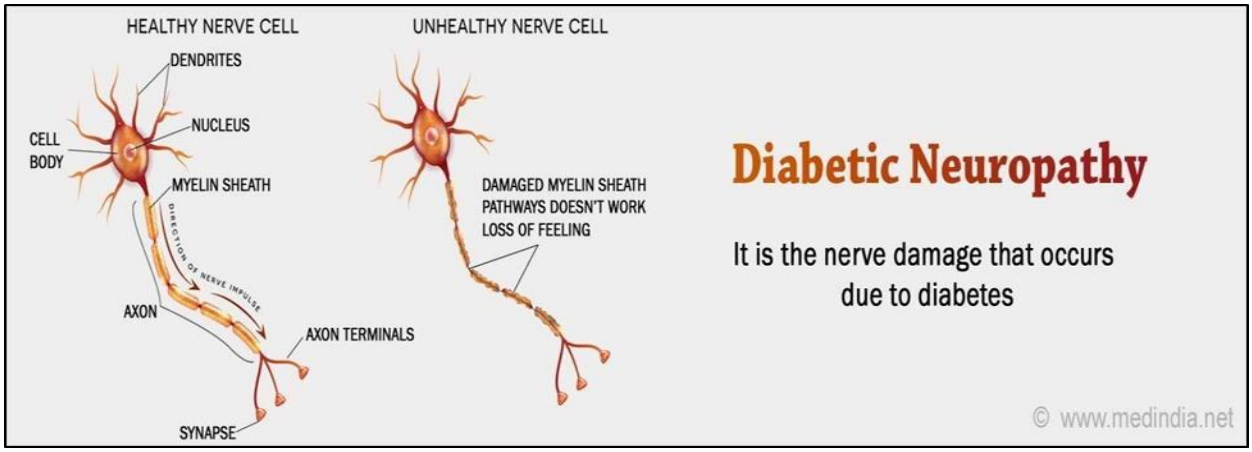


Fig - Diabetic Neuropathy

Types of Diabetic Neuropathy:

Diabetic neuropathy is a group of nerve disorders caused by diabetes. It affects different parts of the nervous system and presents with a wide range of clinical symptoms. The condition is classified into four main types based on the nerves involved and the symptoms presented.

1. **Peripheral Neuropathy (Distal Symmetric Polyneuropathy)**

Peripheral Neuropathy is a condition that results from damage to the peripheral nerves, which are the nerves outside the brain and spinal cord. In diabetic peripheral neuropathy (DPN), high blood sugar levels damage these nerves, especially those in the legs and feet.

Peripheral neuropathy can affect:

Sensory nerves – responsible for feeling (pain, temperature, touch) Motor nerves – control muscles Autonomic nerves – control automatic body functions.[5]

2. **Autonomic Neuropathy:**

- Affects the autonomic nervous system, which controls involuntary bodily functions.
- Can involve cardiovascular, gastrointestinal, genitourinary, and sudomotor systems.
- Symptoms include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, bladder dysfunction, and erectile dysfunction.[6]

3. Proximal Neuropathy (Diabetic Amyotrophy or Lumbosacral Radiculoplexus Neuropathy):

- Less common, but potentially severe.
- Affects nerves in the thighs, hips, buttocks, or legs.
- Usually occurs in older adults with type 2 diabetes.

- Symptoms include sudden, severe pain in the hip or thigh, muscle weakness, and weight loss.
- Often unilateral and may improve over time.[7]

4. Focal and Multifocal Neuropathy (Mononeuropathy):

- Involves damage to a single nerve or nerve group, most often in the head, torso, or leg.
- Commonly affects the cranial nerves (e.g., third cranial nerve palsy).
- Symptoms can include double vision, eye pain, Bell's palsy, or pain in the front of the thigh or chest.[8]
- Sudden onset; typically resolves within weeks or months.

Transdermal Drug Delivery System (TDDS):

Definition: A Transdermal Drug Delivery System (TDDS) is a method of delivering medications through the skin in a non-invasive manner to achieve systemic effects. The drug diffuses through the layers of the skin and enters the bloodstream.[10]

Key Components:

1. **Drug Reservoir** – Contains the active drug.
2. **Rate-controlling Membrane** – Regulates the release of the drug.
3. **Adhesive Layer** – Helps the patch stick to the skin and sometimes also serves as the drug carrier.
4. **Backing Layer** – Protects the patch from the environment.
5. **Release Liner** – Removed before application.

ADVANTAGES:

- Avoids first-pass metabolism.
- Provides controlled and sustained drug release.
- Enhances patient compliance.
- Minimally invasive.

Limitations:

- Only suitable for drugs with low molecular weight and adequate lipophilicity.
- Possible skin irritation or allergic reactions.
- Limited number of drugs suitable for transdermal delivery.

Common Drugs Used:

- **Nicotine** (for smoking cessation)
- **Fentanyl** (pain management)
- **Nitro-glycerine** (angina)
- **Estradiol** (hormone therapy)
- **Clonidine** (hypertension)

Mechanism of Drug Penetration:

Drugs primarily penetrate the skin via passive diffusion through the **stratum corneum**, which is the main barrier. Enhancers (e.g., chemical enhancers, iontophoresis, microneedles) are sometimes used to improve drug permeation.

Benefits of transdermal patch:

1. Pain Relief (Analgesic Effect):

Sweet flag contains active compounds like β-asarone, which have shown analgesic and anti-inflammatory effects. These can help reduce the

burning, tingling, and stabbing pain typical of diabetic neuropathy.

1. **Antioxidant Action**:

Diabetic neuropathy is associated with oxidative stress. Sweet flag has strong antioxidant properties, which help neutralize free radicals and protect nerve cells from damage.

2. **Improved Nerve Function:**

Certain compounds in sweet flag may promote nerve regeneration or repair. Regular use could support functional recovery of damaged peripheral nerves.

3. **Controlled and Sustained Delivery:**

- Using a transdermal patch allows for: Sustained drug release over several hours.
- Bypassing the digestive system, which avoids issues with poor absorption or gastrointestinal side effects.
- Improved patient compliance, especially in those with multiple medications

4. **Anti-inflammatory Effects:**

Sweet flag has anti-inflammatory effects that reduce swelling and discomfort in affected nerves, helping to ease neuropathic symptoms.

Aim & Objective of transdermal patch of calamus oil extract:

Aim:

To develop and evaluate a transdermal drug delivery system containing Acorus calamus Linn. extract for the effective management of diabetic neuropathy, focusing on sustained drug release, improved patient compliance, and therapeutic efficacy.[11]

Objectives:

1. To extract and characterize the bioactive phytoconstituents of Acorus calamus Linn., with an emphasis on its neuroprotective and anti-inflammatory properties.
2. To formulate a transdermal patch incorporating the Acorus calamus extract using suitable polymers and plasticizers to ensure stability, adhesion, and drug release.
3. To evaluate the physicochemical properties of the formulated transdermal patch, including thickness, weight uniformity, folding endurance, moisture content, and drug content.
4. To assess the in vitro drug release profile and permeation characteristics of the patch using appropriate skin models.
5. To perform in vivo studies (if applicable) or simulate pharmacodynamic evaluation to determine the efficacy of the patch in alleviating symptoms associated with diabetic neuropathy.
6. To compare the transdermal patch with conventional formulations in terms of release kinetics and potential therapeutic advantages.[12]

Experiment work:

- **Selection of Herbal material**:

Selection of dried rhizomes of Acorus calamus which contains active ingredients.

- **Extraction Procedure using Steam Distillation Setup:**

1) Allow the chopped rhizome for air drying slightly to reduce moisture content.

2) Assemble a steam distillation unit.

3) Place the chopped sweet flag rhizomes into the distillation chamber.

4) Ensure that there is enough space for steam to pass through the material.

5) Add required amount (50 ml) of water in that distillation Flask.

6) Water is heated in flask to produce Steam

7) The steam is directed into a chamber called that distillation vessel containing the chopped sweet flag rhizome.

8) Steam starts to pass through the plant material.

9) Heat causes the essential oils in the rhizomes to evaporate along with steam.

10) The steam oil vapour mixture passes through a condenser, which cools it down.

11) This turns the vapour back into a liquid mixture of water and essential oil.

12) The liquid mixture flows into a separator.

13) Since the oil and water don't mix and have different density the essential oil floats depending on its density.

14) The oil is then collected separately.

15) The yield essential oil from sweet Flag is relatively low (typically around 1-3% of dry weight).[22][23]

Basic Tests for Sweet Flag Essential Oil (Calamus Oil):

Parameter	Procedure	Result
Physical Properties	Colour Odour Appearance	Pale yellow to light brown. Warm, spicy, woody scent with a slightly bitter note (distinctively aromatic). Smooth, uniform, and flexible film
Solubility Test	Test: Add a few drops of calamus oil to a test tube with water — it should float and not dissolve. Add to ethanol — it should dissolve with slight turbidity or clear.	Essential oils are generally not soluble in water but soluble in alcohol (like 70% or 90% ethanol).

Fig No:8 – Evaluation test for sweet flag essential oil.

Tests for calamus oil were performed successfully.

Formulation table for Transdermal Patch:

Sr No	Ingredients	Quantity taken	Approx % w/w
1	Asaron Oil	3ml	3 %
2	Glycerine	2ml	0.2 %
3	Methyl Paraben	0.5gm	0.1 %
4	Ascorbic Acid	1gm	1 %
5	Gelatine	3.5gm	3.5 %
6	Ethanol	3.5ml	3.5 %
7	Water	Q.S up to 100ml	Q. S

Fig No: 9- Ingredients and quantity taken.

Procedure:

a) Use a digital balance to precisely weigh each ingredient.

b) Set the magnetic stirrer on top of the beaker.

c) Fill the beaker with the necessary volume of water and 3.5 grams of gelatine.

d) Position the magnetic bead in the beaker's middle.

e) Use a heat regulator to raise the temperature to 40°C. Additionally, the bead's side-by- side rotation should be preserved.

f) Set another beaker on a different magnetic stirrer side by side, then add ethanol and Acorus calamus extract oil to ensure the oil dissolves completely.

g) Add the paraben and 1 gram of ascorbic acid when the gelatine has completely melted in the water.

h) Transfer the sample to a different beaker containing the active medicinal ingredient after the combination has a semi-solid texture.

i) Give it five minutes to thoroughly combine.

j) Put the butter paper in the petri dish, then cover it with glycerine and use a spreader to evenly distribute it.

k) Using a spreader, pour the mixture onto butter paper.

l) Give it 5 to 6 hours to dry.

m) Cut the patch to the appropriate size (e.g., 1 cm^2, 2 cm^2) after it has dried.

n) Apply the baking layer.

o) Store the patches in airtight containers or between release liners to prevent moisture absorption.

p) Keep in a cool, dry place until evaluation.[24][25]

Evaluation of transdermal patch containing calamus oil extract:

A. Organoleptic Evaluation:

Organoleptic evaluation refers to the assessment of a product using the human senses primarily sight, touch, smell, and occasionally taste (though taste is not applicable for transdermal patches).

Sr No	Organoleptic evaluation	Patches		
		P1	P2	P3
1	Colour	Brownish red	Brownish red	Brownish red
2	Odour	Strong, aromatic, and slightly spicy	Strong, aromatic, and slightly spicy	Strong, aromatic, and slightly spicy
3	Appearance/Shape	Thin layered	Thin layered	Thin layered

B. Thickness measurement test:

The thickness test is a critical physical evaluation parameter used to measure the uniformity and consistency of transdermal patches. Uniform thickness ensures consistent drug release and skin contact.

Purpose:

To confirm that the patch has uniform thickness throughout.

To ensure consistent drug dosage and release profile.

To detect any manufacturing defects such as layering issues or air bubbles.

Procedure:

Instrument Used:

A digital micrometre, vernier calliper, or screw gauge with high precision (usually up to 0.01 mm).

Sample Preparation:

Select patches randomly from a batch.

Ensure they are free from dust and handled gently.

Measurement:

- Measure the thickness at multiple points (usually three to five) on each patch
- centre and corners.
- Average the values to obtain the mean thickness.
- **Units:**

Reported in millimeters (mm) or micrometers (µm).

Sr no	Patch thickness(mm)	Mean value (thickness)
1	0.42	0.41mm
2	0.41	
3	0.41	

A. pH test for evaluation:

Purpose:

To determine the acidity or alkalinity of the aqueous solution of the plant material. This helps in assessing the quality and stability of the crude drug.

Procedure:

Sample Preparation:

- Take about 1 gram of the powdered Sweet Flag rhizome.
- Boil it with 100 ml of distilled water for about 5–10 minutes.
- Cool and filter the solution.

pH Measurement:

Use a pH meter (or pH indicator paper for approximate value). Dip the electrode of the pH meter into the filtered solution. Record the pH value.

Expected Result:

The pH value of Sweet Flag extract typically lies between 5.0 to 7.0, indicating a slightly acidic to neutral nature.

Significance:

A consistent pH range indicates good quality and helps in maintaining the shelf life of formulations. Deviation from standard pH may indicate adulteration, deterioration, or improper storage.

Sr no	Patches	pH Observed
1	P1	6.77
2	P2	6.55
3	P3	6.49

B. Moisture Content:

Moisture content in a sweet flag (Acorus calamus) transdermal patch refers to the amount of water retained in the patch formulation after its preparation and during storage. It is a critical parameter in evaluating the stability, shelf life, and effectiveness of the patch.

Measurement of Moisture Content:

Common methods:

Gravimetric Method (Loss on Drying): The patch is weighed before and after drying in an oven at a

specific temperature (e.g., 100–105°C for 1–2 hours).

Formula:

Moisture content (%) = Initial weight - Final weight/ Initial weight × 100

- Karl Fischer Titration: A more precise chemical method to measure low levels of moisture.
- Factors Affecting Moisture Content in the Patch:
- Polymer Type and Ratio: Polymers like PVA, PVP, HPMC etc., have different water-retention capacities.
- Plasticizers: Glycerine, PEG, and propylene glycol can hold moisture and influence the final content.
- Environmental Conditions: Humidity and temperature during drying, storage, or handling affect residual moisture.
- Drying Method: Oven drying, vacuum drying, or air drying all yield different moisture levels.

Acceptable Moisture Content Range

- Typically ranges between 2% to 15%, depending on the formulation.
- Too low: risk of cracking or loss of flexibility.
- Too high: risk of microbial growth and poor adhesion.[24][25]

Sr no	Patches	Moisture Content (%)
1	P1	13.21
2	P2	13.45
3	P3	14.22

RESULT:

The transdermal patch was successfully formulated using the solvent casting method. By using the gelatine as biodegradable and biocompatible polymer, and glycerine was used as a plasticizer. The patches were smooth, flexible, and uniform in thickness. Evaluation parameters included:

Thickness:0.4mm

pH: 6.6

Moisture Content:13.6

CONCLUSION:

The successful formulation of a transdermal patch using sweet flag (Acorus calamus) extract marks a significant advancement in the alternative management of diabetic neuropathy. The patch exhibited desirable physicochemical characteristics, consistent drug content, sustained release, and good mechanical strength. These therapeutic effects can be attributed to the bioactive compounds, particularly β-asarone and eugenol, present in the Acorus calamus extract. The transdermal route further enhances patient compliance by offering non-invasive, controlled drug delivery with minimal side effects. This study supports the potential of sweet flag-based transdermal systems as a promising herbal intervention for alleviating diabetic neuropathy, paving the way for future clinical research and development.

DISCUSSION:

The current study focused on the formulation and evaluation of a transdermal patch containing Acorus calamus (commonly known as Sweet Flag) extract using gelatine as a natural polymer. The primary aim of the study was to explore the potential of the herbal patch as an alternative therapeutic system for managing diabetic neuropathy, based on phytochemical knowledge and in vitro evaluation, without involving animal or human models. Transdermal patches have gained prominence as a non-invasive drug delivery

method, offering benefits such as steady drug release, improved bioavailability, and patient compliance—especially in chronic conditions like diabetic neuropathy. In this formulation, gelatine was selected as the film-forming polymer due to its biodegradability, biocompatibility, film-forming ability, and natural origin, making it suitable for delivering herbal actives through the skin.

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Conflict of interest:

The author declared no conflict of interest with respect to the authorship and publication of this article.

Availability of data and material:

All the data used in our article are available from publically accessible sources such as PubMed, Elsevier, Wikipedia, etc.

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