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Review Article

Formulation and Evaluation of Diclofenac Sodium Transdermal Patches for Dysmenorrhea

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Abstract

Dysmenorrhea, characterized by painful menstruation, poses a significant burden on women's health and well-being. Diclofenac sodium, a potent nonsteroidal anti-inflammatory drug (NSAID), offers a promising approach for managing dysmenorrhea through its analgesic and anti-inflammatory properties. This abstract aims to evaluate the efficacy and safety of diclofenac sodium patches specifically in treating dysmenorrhea, drawing insights from available literature. Clinical trials and studies have demonstrated the effectiveness of diclofenac sodium patches in providing sustained pain relief and improving menstrual symptoms associated with dysmenorrhea. By delivering the drug transdermally, these patches offer targeted relief directly to the site of pain, bypassing gastrointestinal metabolism and potentially minimizing systemic adverse effects. Additionally, the convenience and ease of application make diclofenac sodium patches a favourable option for women seeking non-oral alternatives for managing menstrual pain. Despite the generally favourable safety profile observed in studies, careful monitoring is warranted to mitigate potential adverse effects, particularly skin irritation or allergic reactions. Overall, diclofenac sodium patches emerge as a promising and well-tolerated therapeutic option for effectively alleviating dysmenorrhea and enhancing the quality of life for women experiencing menstrual discomfort.

Keywords: Diclofenac Sodium; Dysmenorrhea; Non-Oral Alternatives

Introduction

Transdermal drug delivery system (TDDS) is a method of administering medication through the skin for systemic distribution, bypassing the gastrointestinal tract and liver metabolism. It typically involves the application of a patch containing the drug, which gradually releases the medication into the bloodstream over a specified period. It has emerged as a promising alternative to traditional routes of drug administration such as oral or injectable methods. TDDS offers advantages such as improved patient compliance, reduced side effects, and sustained drug release, making it suitable for various therapeutic applications.

Advantages

Transdermal drug delivery systems offer several advantages:

- **Non-Invasive:** They don't require needles or invasive procedures, making them more convenient and comfortable for patients.
- **Steady Drug Release:** They provide a controlled and continuous release of medication over an extended period, ensuring stable blood levels and minimizing side effects.
- **Avoidance of First-Pass Metabolism:** Drugs bypass the gastrointestinal tract and liver, avoiding degradation and increasing bioavailability.

- **Patient Compliance:** Transdermal patches are easy to apply and require less frequent dosing, improving patient adherence to medication regimens.
- **Reduced Side Effects:** By bypassing the digestive system, they can reduce gastrointestinal side effects associated with oral medications.
- **Improved Safety:** Transdermal delivery systems offer a reduced risk of overdose or under dose compared to oral medications.
- **Localized Treatment:** Some transdermal patches can deliver medication directly to the affected area, providing targeted therapy.
- **Convenience:** They offer convenience for patients who may have difficulty swallowing pills or who require long-term medication administration.
- **Stable Plasma Levels:** Transdermal delivery can maintain steady plasma drug levels, reducing the need for frequent dosing adjustments.
- **Versatility:** Transdermal delivery can be used for various types of drugs, including those for pain management, hormone replacement, and nicotine replacement therapy.

Diclofenac sodium

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) used to relieve pain, inflammation, and swelling caused by various conditions such as arthritis, gout, and sprains. It works by inhibiting the production of certain chemicals in the body that cause inflammation and pain. Diclofenac is available in various forms including tablets, capsules, gels, patches, and injections. It has some potential side effects such as stomach ulcers, bleeding, and kidney problems, especially with long-term use or at high doses. It's typically not recommended for use in the third trimester of pregnancy and caution should be exercised in individuals with a history of gastrointestinal issues or cardiovascular disease.

Menstrual cramps

Menstrual cramps, medically known as dysmenorrhea, are a common discomfort experienced by many individuals with menstruating reproductive systems. These cramps typically occur just before or during menstruation and are often characterized by lower abdominal pain or discomfort, although they can also manifest as back pain or radiate down the thighs. Menstrual cramps result from the uterus contracting to shed its lining, which can cause discomfort ranging from mild to severe. Various factors, including hormonal changes, prostaglandin levels, and underlying health conditions, can influence the severity of menstrual cramps.

Use of diclofenac patch in managing dysmenorrhoea

Diclofenac sodium patches are sometimes used for dysmenorrhea, which is menstrual pain. The patches contain diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting the enzyme cyclooxygenase (COX). This inhibition reduces the production of prostaglandins, which are chemicals in the body that cause inflammation and pain. By decreasing prostaglandin levels, diclofenac helps to alleviate menstrual pain. The patch form allows for a controlled release of the medication over time, providing sustained relief from symptoms.

History

The era of transdermal drug delivery began in the 20th century with the development of adhesive patches containing medication. One of the earliest examples was the Scopolamine patch introduced in the 1970s for motion sickness. Since then, researchers have made significant advancements in formulations, patch designs, and delivery technologies, expanding the range of drugs that can be delivered through the skin. Today, transdermal patches are used to administer medications for conditions such as pain, hormone therapy, smoking cessation, and cardiovascular diseases, etc.

TDDS classification

They can be classified based on various factors, including the mechanism of drug delivery, type of patch, and production methods.

Based on mechanism of drug delivery

- **Matrix Systems**: These systems involve the drug being dispersed within a polymeric matrix, which controls its release rate. Examples include reservoir-type patches.
- **Reservoir Systems:** These contain a drug reservoir separated from the skin by a rate-controlling membrane. The drug is released from the reservoir through the membrane.
- **Drug-in-Adhesive Systems:** Here, the drug is dispersed within the adhesive layer of the patch, which adheres to the skin. Drug release occurs through the adhesive layer.
- **Drug-in-Membrane Systems:** In these systems, the drug is dispersed within a membrane that controls its release rate. The membrane is in direct contact with the skin.

Based on type of patch

- **Single-layer patches:** These contain the drug within a single layer.
- **Multi-layer patches:** These consist of multiple layers, each serving a specific function such as drug reservoir, adhesive, and backing layer.
- **Drug-in-polymer matrix patches**: The drug is dispersed within a polymeric matrix, which is in direct contact with the skin.

Based on production methods

- **Solvent casting method:** In this method, a solution of the drug and polymers is cast onto a substrate, and the solvent is evaporated to form the patch.
- **Hot-melt extrusion:** This process involves melting the drug and polymer mixture and extruding it through a die to form a solid matrix, which is then cut into patches.
- **Compression moulding:** The drug and polymer mixture is compressed into a mould under high pressure and temperature to form the patch.
- **Microneedle-based systems:** These involve the use of microneedles to create micro channels in the skin, allowing for enhanced drug delivery.

Types of transdermal patch

They come in various types, designed to deliver different medications through the skin. Some common types include:

- **Drug-in-Adhesive Patch:** These patches contain the drug within the adhesive layer, which sticks to the skin. The drug is released gradually over time.
- **Matrix Patch**: In these patches, the drug is dispersed within a polymer matrix. The drug diffuses through the matrix and into the skin.
- **Reservoir Patch:** These patches have a drug reservoir separated from the skin by a rate-controlling membrane. The drug is released from the reservoir through the membrane.
- **Vapor Patch:** These patches contain volatile substances that evaporate and are absorbed through the skin. They are often used for delivering aromatherapy or natural remedies.
- **Iontophoretic Patch:** These patches use a small electrical current to drive charged medication molecules through the skin.
- **Micro-needle Patch**: These patches contain tiny needles that painlessly penetrate the skin to deliver medication to the underlying tissue.

Different types of cramps

Cramps are involuntary muscle contractions that can cause pain and discomfort. There are several types of cramps, some of them are:

- **Muscle Cramps:** These are the most common type and can occur in any muscle. They often result from overuse, dehydration, electrolyte imbalances (especially low levels of potassium, calcium, or magnesium), or poor circulation.
- **Menstrual Cramps:** Also known as dysmenorrhea, these cramps occur in the lower abdomen just before or during menstruation. They are caused by the uterus contracting to expel its lining.
- **Exercise-Associated Muscle Cramps (EAMC):** These cramps happen during or after intense physical activity. They're thought to be caused by muscle fatigue, dehydration, or electrolyte imbalances.
- **Gastrointestinal Cramps:** These cramps occur in the abdomen and are associated with conditions like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), or food poisoning.
- **Writer's Cramp:** Also known as hand dystonia, this type of cramp affects the muscles of the hand and forearm, often occurring during repetitive hand movements like writing or typing.
- **Leg Cramps:** These cramps occur in the muscles of the legs, often during the night. They can be caused by muscle fatigue, dehydration, or underlying conditions like peripheral artery disease (PAD) or restless legs syndrome (RLS).
- **Charley Horse:** This term is often used colloquially to refer to a sudden and painful muscle spasm, typically in the legs, especially the calf muscles. They can be caused by dehydration, muscle fatigue, or electrolyte imbalances.
- **Abdominal Cramps:** These cramps can be caused by a variety of factors, including menstrual periods, gastrointestinal issues, urinary tract infections, or even stress.

Drugs available in transdermal patch form

Some drugs commonly available in transdermal patch form, along with their dosage forms and some disadvantages.

Formulation of diclofenac sodium transdermal patch Materials

For the formulation of patch, materials required are –drug, polymer matrix, solvent, penetration enhancer are used.

S. No.	Drugs	Uses	Dose	Disadvantages
1.	Nicotine	Used for smoking cessation.	7 mg - 21 mg per patch	Skin irritation or allergic reactions at the application site, and some users may experience vivid dreams or sleep disturbances.
2.	Fentanyl	Used for managing severe chronic pain.	12 mg - 100 mg/hr	Risk of overdose if not used properly, potential for respiratory depression, skin irritation, and the potential for abuse or diversion.
3.	Estradiol	Used in hormone replacement therapy for menopausal symptoms.	0.025 mg - 0.1 mg per patch	Skin irritation, breast tenderness, nausea, and an increased risk of blood clots, stroke, and breast cancer in some women.
4.	Rivastigmine	Used for treating Alzheimer's disease ad dementia associated with Parkinson's disease.	4.6 mg - 13.3 mg per 24 hours	Includes skin irritation, nausea, vomiting, diarrhoea, and potential for drug interactions with other medications.
5.	Testosterone	For hormone replacement therapy in men with low testosterone levels.	2.5 mg - 10 mg per patch	Acne, headache, mood swings, skin irritation, and the potential for transfer of testosterone to others through skin contact.
6.	Clonidine	Used for managing hypertension and certain neurological conditions such as ADHD.	0.1 mg - 0.3 mg per patch	Dry mouth, drowsiness, dizziness, skin irritation, and rebound hypertension if the patch is stopped abruptly.
7.	Scopolamine	Used to prevent motion sickness and nausea.	0.5 mg -1.5 mg applied every 3 days	Dry mouth, blurred vision, drowsiness, confusion, and skin irritation.
8.	Lidocaine	For localized pain relief, such as post herpetic neuralgia.	30 mg - 150 mg over 12 hrs	Allergic reactions, skin irritation, and in rare cases, systemic toxicity if too many patches are applied or left on for too long.

Table 1: Detailing of various available marketed patches along with their dose and uses.

S. No.	Ingredients	Activity
1.	Diclofenac sodium	Active Ingredient (Drug)
2.	HPMC	Polymer
3.	Polyvinyl Pyrrolidine	Copolymer
4.	Propylene Glycol	Plasticizer
5.	Sodium Lauryl Sulphate	Penetration enhancer
6.	Chloroform : Methanol	Solvent

Table 2: List of ingredients with their activity.

Procedure

The HPMC and polyvinyl pyrrolidine were accurately weighed and dissolved in mixture of Methanol: Water (solvent).

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The drug then dispersed in the polymeric solution and plasticizer of propylene glycol and permeation enhancer of sodium lauryl sulphate was added with continuous stirring using a magnetic stirrer to obtain homogeneous mixture.

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Spread the glycerin into petridish and the resulting mass were poured into the petridish.

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Left the petridish undisturbed at room temperature for 24 hours.

↓

This patch will obtained intact by slowly lifting from the petridish and transdernal patches were cut into radius of 2cm sq.

Figure a

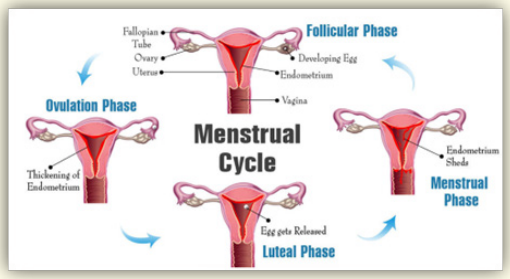

Figure 1: Phases of Menstrual Cycle.

S.NO	Ingredients	F1	F2	F3
1.	Diclofenac sodium	10	10	10
2.	HPMC	200	300	400
3.	Polyvinyl Pyrrolidine	200	200	200
4.	Propylene Glycol	1.2	1.2	1.2
5.	Sodium Lauryl Sulphate	1.2	1.2	1.2
6.	Chloroform : Methanol	1:4	1:4	1:4

Table 3: Formulation Design of Diclofenac Sodium patch.

Evaluation and characterization

The efficacy of diclofenac patches depends on factors such as patch design, skin permeability, and the individual patient's response to the medication.

Physical appearance

All the patches were visually observed, inspected for colour, flexibility, smoothness, etc. They often have a semi-transparent or opaque backing to protect the medication and an adhesive side that sticks to the skin.

Thickness of patch

The thickness of each patch was measured by using digital micrometer at three different points. Micrometer is a tool that measures the size of a target by enclosing it. Some models are even able to perform measurements in units of 1 µm. Unlike hand callipers, micrometers adhere to Abbes' principle, which enables them to perform more accurate measurements.

Weight uniformity

The uniformity of weight was calculated by weighing3 difference patches and the average was taken.

Folding endurance

A part of patch is to be cut evenly and repeatedly folded at same place until it breaks. The result indicates that the patches wouldn't break and can withstand the normal handling and application.

Moisture content

Place the patch in the analyzer or desiccator for 24 hrs and measure the change in weight before and after drying. The percentage moisture absorbed was calculated by the below mentioned formula:

Moisture content = Final weight – Initial weight × 100 / Initial weight

Figure 2: Prepared diclofenac Patch.

Figure 3: Measurement of thickness of patch.

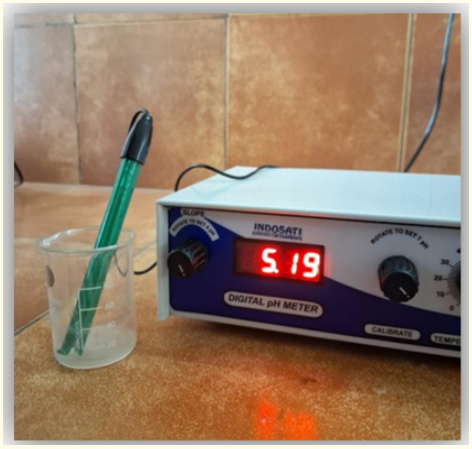

Figure 4: Determination of pH.

Results and Discussion

The study shows the physical appearance of Diclofenac Sodium Transdermal Patch is off-white in colour, smooth in texture and round in shape. On comparison of prepared patch and marketed patch of Diclofenac sodium, the thickness and folding endurance of prepared patch is found to be similar to the marketed patch. The study seemed that as the concentration of polymer increases the thickness of patch, weight uniformity, folding endurance increases. The evaluation studies show that the patch formulation F1 having less thickness, high folding endurance, less moisture content, and have optimum uniformity of weight characteristics as compared to other formulations (F1-F3). The present work can further be proceeding with in-vivo study on healthy animals to evaluate the pharmacokinetic profile [1-18].

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