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Review Article

A REVIEW ON TRANSDERMAL PATCHES USED AS AN ANTI-INFLAMMATORY AGENT

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ABSTRACT

The transdermal drug delivery system is widely accepted due to its numerous advantages as it is a non-invasive drug administration process with prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance, and easy termination of drug therapy. Non-steroidal anti-inflammatory drugs such as Diclofenac sodium, Lornoxicam, Aceclofenac, Ibuprofen, antihypertensive drugs, for example, Repaglinide, Atenolol, and Antiviral agents such as Stavudine, zidovudine represents the most commonly used medications for the treatment of pain and inflammatory reaction but various side effects can limit their use. Therefore, transdermal delivery of these drugs has advantages of avoiding hepatic first-pass effect, gastric irritation and delivering the drug for an extended period of time at a sustained level. The present article mainly focuses on the work been done on these drugs by formulated and delivered as transdermal patches to decrease the side effects related to the oral delivery.

Keywords: Transdermal patch, Non-steroidal anti-inflammatory drugs, Repaglinide, Diclofenac sodium, Inflammation.

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INTRODUCTION

Inflammation

Inflammation is a process that occurs after an infection or tissue injury. The inflammatory response is essential in maintaining homeostasis which leads to tissue damage due to fibroplasia, leukocytosis, excessive production of cytokines and other mediators such as tumor necrosis factor-α-alpha, interleukin (IL)-6, and IL-8. Inflammation is also an important physical factor that triggers the immune reaction [1]. Superficial pain arises from nociceptive receptors in the skin and mucous membranes and is often associated with inflammation and tissue swelling [2]. In general, non-steroidal anti-inflammatory drugs (NSAIDs) can be used for the treatment of pain and inflammation. The NSAIDs can inhibit the activity of cyclooxygenase enzymes (COX-1 and COX-2) and therefore inhibit the synthesis of thromboxanes and prostaglandins (PGE_2) [3]. COX enzyme is released during pain and inflammation, whereas thromboxanes and PGE_2 are considered as the mediators of allergic reactions such as vasoconstriction and inflammation. [4]. Example of some commonly used NSAIDs includes aspirin, ibuprofen, naproxen and diclofenac. Diclofenac is used for the treatment of mild to moderate muscular pain and to alleviate the symptoms of arthritis, menstrual cramps, toothache and migraines/headaches [5]. However, if it is taken orally for a long period of time in high doses then it may lead to fatal stomach, intestinal bleeding and heart attack or stroke [6].

As an alternative to oral drug delivery and parenteral administration for NSAIDs, now a days Transdermal drug delivery (TDD) is mostly preferred reasons [7]. Among the various advantages, one advantage is that the transdermal route avoids the metabolism of the drug inside the liver and its rapid absorption inside the gastrointestinal (GI) tract, thus avoiding the risk of internal bleeding and irritation. In the TDD systems, drugs are specifically designed to deliver a predestined amount of drug through the stratum corneum and the systemic circulation [8]. The choice of drug for TDD depends on the size of the drug, as it can pass through the skin pores. However, improper use of the strong ointments can potentially lead to skin allergies, dryness, lesions, and thinning of the skin [9].

In TDDS systems mostly drug-loaded patches, backing films, microneedles, thermal, mechanical and electrical ablation, are often preferred [10]. For treatment of muscular pain, a few transdermal patches are available on the market and these are mostly based on either narcotic (Fentanyl) or methyl salicylate (Salonpas), which can cause breathing problems, or toxicity issues [11,12]. TDD system allows the administration of potent drugs with the benefit of self–administration and enhanced therapeutic efficacy [13].

It is caused by injury to the living tissue. It involves the 4 primary indicators of inflammation that is pain, redness, heat, swelling. The role of inflammation such as healing, restorative process and also having an aggressive role, which is more widely recognized [14].

Inflammation is a programmed local tissue response

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Peculiar to vascularized living tissue

The inflammatory response involves different events which can be elicited by numerous stimuli, for example, chemical, thermal injury and antigen-antibody interactions. The different events of inflammation are underlined different manifestations that is induced and regulated by a large number of chemical mediators, eicosanoids, kinins, etc. [14]. The main aim of inflammatory response is to localize and eliminates the harmful agents; secondly remove the damaged tissue components to culminate in the healing of the affected tissues [15].

THE INFLAMMATORY RESPONSE

PGE_2 has various physiological roles including regulation of normal body temperature, renal blood flow, gastric mucosal integrity, etc. The pathway of PGs synthesis starts with the generation of arachidonic acid from cell membrane phospholipid by PLA2. Then, arachidonic acid is converted to PGs by the enzyme COX. Mostly the inducible enzyme COX-2 is acting as the most active during inflammatory processes. LTs are produced by the enzyme 5-lipooxygenase. It is highly associated with an inflammatory condition that is nitric oxide synthase which produces NO and causes inflammation. According to the WHO, in 2018 approx 235 million people suffer from inflammation in the world. The symptomatic relief provides relief to the patient suffering from inflammatory autoimmune diseases (Fig. 1).

Inflammation is classified into two types

- Acute inflammation
- Chronic inflammation.

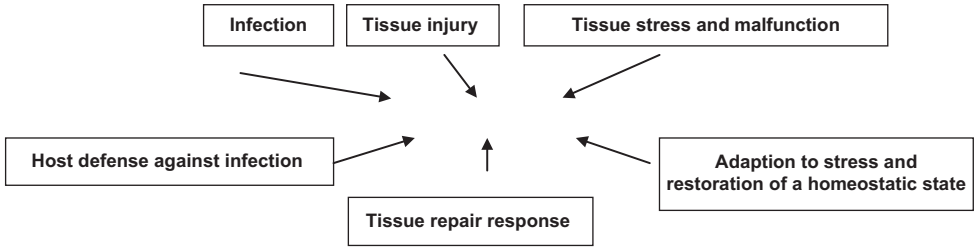

Fig. 1: Inflammatory responses

Acute inflammation is defined as a rapid response to a harmful agent that serves to deliver mediators of host defense, leukocytes, and plasma proteins to the site of injury. It gives an initial response of the body to harmful stimuli [16].

ACUTE INFLAMMATION HAS 3 MAJOR COMPONENTS

- Alterations in the vascular caliber that lead to an increase in blood flow
- Structural changes in the microvasculature that permits plasma proteins and leukocytes to leave the circulation
- Leucocyte emigrates from the microcirculation, their accumulation within the focus of injury and their activation to eliminate the offending agent.

CHEMICAL MEDIATORS OF ACUTE INFLAMMATION

- Histamine: increased permeability
- PGE_2: vasodilation
- Leukotrienes: increased permeability.

Morphology of acute inflammation

- Pseudomembranous inflammation

It is an inflammatory response of the mucous surface to toxins of diphtheria or irritant gases.

- Ulcer

Ulcers are local defects on the surface of an organ produced by inflammation.

- Cellulitis

Due to the spreading effects of substances such as hyaluronidase released by some bacteria, diffuse inflammation of soft tissues can take place [17].

Chronic inflammation can be defined as a prolonged process in which tissue destruction and inflammation occur at the same time. In general, for chronic inflammation, the extent and effects of inflammation may vary with the cause of the injury and the ability of the body to repair and overcome the damage. In this inflammation process, the inflammatory response is out of a fraction resulting in damage to the body [18]. Common symptoms of chronic inflammation are fatigue, fever, mouth sores, rashes, abdominal pain, etc. In chronic inflammation, disorders, such as arthritis and hemorrhoids, that continued to torment humanity despite nature's endowment of medicinal plant resources (Fig. 2) [19].

GENERAL FEATURES OF CHRONIC INFLAMMATION

- Mononuclear cell infiltration: phagocytes, circulating monocytes, macrophages, etc.
- Tissue destruction or necrosis
- Proliferative changes: small blood vessels and fibroblasts.

Nonsteroidal anti-inflammatory drugs are the agents which suppresses the inflammation. These agents have also adverse effects such as peptic ulceration and osteoporosis [20]. NSAID'S are one of the common therapeutic agents used for the treatment of pain, fever, and inflammation. Examples: Diclofenac, Ibuprofen, Naproxen, and Celecoxib [21].

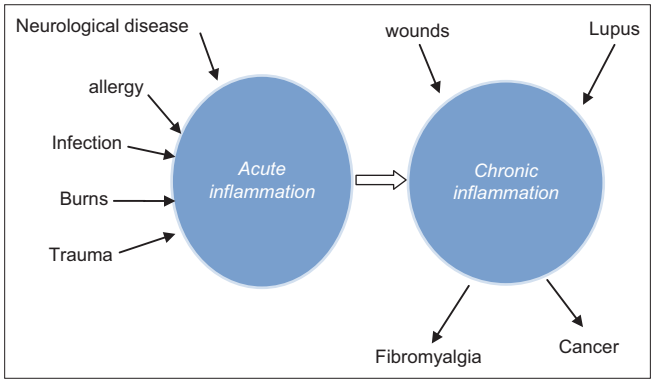

Fig. 2: Causes of acute and chronic inflammation

In this review, we are discussing the different types of the transdermal patchs.

TRANSDERMAL PATCH

The Transdermal patch is medicated adhesive patch. These are prepared which deliver a therapeutically effective amount of drugs across the skin. The patches provide a controlled release of the medication into the patient (Fig. 3).

It acts as a carrier for a drug which holding it until the point of application. At this point, the adhesive secures the patch to the skin. It allows the drug access to the skin, it helps the permeation process. It delivers the drugs topically. A transdermal patch containing a high dose of drug into the skin which is retained for a prolonged period of time, gets entered the blood flow through the diffusion process.

Advantages

1. Self- medication is possible
2. Unwanted side effects get minimized
3. First pass metabolisms of drug get avoided.

Disadvantages

1. Larger molecules size of the drug creates difficulty in absorption
2. Chances of allergic reactions at the site of applications such as itching, rashes, etc.

Transdermal drug administration generally refers to the topical application which intact in the skin simultaneously minimizes the retention and also metabolism of the drug in the skin. TDD systems are used in the skin disorders, pains, angina pectoris, neurological disorders, etc. TDD systems are considered as the new drug delivery systems which involve the demonstration of clinical safety and effectiveness of the drug. In novel techniques, drug delivery has been investigated in human medicine in recent years. Among the new drug delivery systems, there are mostly used for transdermal applications [21].

Limitations of TDD systems

- It cannot administer drugs that require high blood levels
- Drug formulation may cause irritation or sensitization.

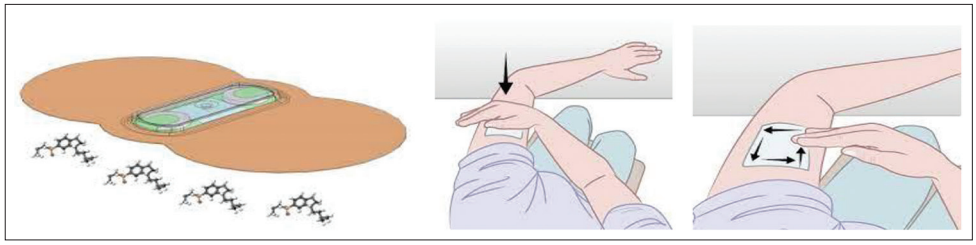

Fig. 3: Types of patchs

Components of transdermal patches

The basic components of transdermal patches are consist of a polymer matrix, drug reservoir, active ingredient, permeation enhancers, backing laminates, adhesives, plasticizers, solvents, etc. [22].

Transdermal patches are categorized into 3 categories

- First -generation
- Second generation
- Third generation.

In the 1st generation transdermal patches, it is used in clinics. These are consisting of the drug in a reservoir that is enclosed by one side with impermeable adhesives. In the 2nd generation, the transdermal patches increased the skin permeability which reduces damage to deeper tissues. Again In the 3rd generation, the transdermal patches increased the skin penetration of drugs which also protect the deeper tissues [22]. Transdermal patches are generally provided constant blood levels but avoid the first-pass metabolism. It increased patient compliance.

Method of preparation of transdermal patches

- Asymmetric TPX membrane method
- Circular teflon mould method
- EVAC membrane method
- Mercury substrate method.

Selection of drug candidate for the transdermal delivery system

The drug candidate should be:

- Adequate skin permeability
- Adequate skin acceptability
- Adequate clinical need.

Examples of transdermal patches

Transdermal patch of diclofenac sodium

It has been investigated that diclofenac sodium patches using chitosan and polyvinyl alcohol (PVA) cross-linked tripolyphosphate sodium to increased transdermal permeation of the drug from the matrix system across rabbit skin.

The investigation of diclofenac sodium patch was done by ultraviolet spectrophotometry. Determination of physical characteristics of the film includes the weight test, thickness, organoleptic observation, interaction between materials used in Fourier transform infrared (FTIR). It has been observed that the result of physicochemical parameters of the transdermal patches has been found satisfactory. The FTIR data of rabbit skin indicated chitosan and PVA alcohol cross-linked TPP increases transdermal permeation of Diclofenac sodium in the stratum corneum [23]. An ideal transdermal patch should have flexibility, elasticity, and softness and at the same time must have sufficient strength to follow the body contours. It also has good adhesive strength for prolonged retention on the skin for the desired duration of action. In addition, various permeation enhancers and chemicals are used to improve penetration across the skin, including alcohols, terpenes, and surfactants [24,25].

Postsurgical pain has often been a nemesis for surgeons and patients alike due to a considerable degree of inflammatory response involved. NSAIDs are among the most generally utilized medication as because they decrease the inflammatory responses [26]. Diclofenac sodium, an aryl acetic acid derivative is the regularly utilized NSAID either as a sole agent or in combination with different NSAIDs [5]. It is a nonselective cox inhibitor (conventional NSAID) that acts by inhibiting COX enzyme [27]. A benefit of a transdermal medication over different kinds such as oral, skin, and so on, is that it gives a controlled release of the medicament into the circulation [11]. The transdermal diclofenac patch (Nu Patch) is utilized to relieve postoperative pain. It is applied once for the span of 24 h and produces quick relief from discomfort with negligible or no side effects. The patch is to be applied on the skin, ideally in a space without any hair [28]. The patch achieves plasma levels ranging between 20 and 50 ng/ml and it is lesser when compared to the oral route [29].

Transdermal gel patch of lornoxicam (LRX)

LRX is a potent NSAID that belongs to oxicam class. It is mainly used in chronic pain and inflammatory conditions. It also shows numerous GI, renal, and hematological adverse effects when taken orally [30]. Frequent administration of LRX is required due to its short half-life (3–4 h). However, in the case of chronic conditions parenteral administration is not recommended [31]. Oleic acid (OA) has been widely used for improving percutaneous drug absorption. It has been proved that the use of OA with propylene glycol gives satisfactory results in many transdermal formulations [24,32,33]. LRX, similar to other NSAIDs, decreases the PGE_2 synthesis by inhibiting both isoforms of the COX enzymes in the same proportions [34]. Inhibition of (PG) synthesis help to protect the gastrointestinal mucosal membrane by preventing the gastric acid secretion and it also strengthened the mucosal barrier for gastric acid. However, the inhibition of PG synthesis may cause heartburn, mild dyspepsia, ulceration, and hemorrhage [35].

Sodium alginate is a biopolymer that has been widely used as a binding and disintegrating agent in the formulation of tablets [36,37]. Sodium alginate has a unique ability to form gel in the presence of calcium chloride, and it also delays the dissolution of a drug from sustained -release formulations [38]. The permeation enhancers are used to facilitate the transdermal delivery of hydrophilic and lipophilic medications, for example, dimethyl sulfoxide [39]. The membrane-based transdermal patches for LRX gel have been studied using OA and polypropylene glycol as penetration enhancers to improve the drug delivery across the skin and also evaluated the *In vivo* analgesic and anti-inflammatory activity. It has been previously demonstrated that the fabricated transdermal gel patch of LRX can deliver the drug through the skin in a controlled release manner with desired anti-inflammatory activity [40].

Transdermal patch of repaglinide

The transdermal patch of repaglinide has been prepared to sustain the release and improve the bioavailability of drug and patient compliance. The formulations were prepared by solvent casting method. The prepared formulations were evaluated for various parameters such as tensile strength, %drug content, %moisture content, and folding endurance. Repaglinide has the half- life of 1 h, bioavailability in the body is 56% due to first-pass metabolism [41]. Diabetes mellitus is a chronic metabolic disorder mainly caused by hyperglycemia caused by insulin deficiency, and it is often combined with insulin

resistance [42]. Repaglinide belongs to meglitinide class of drugs used to treat noninsulin-dependent diabetes mellitus. Repaglinide is generally given in a dose of 0.5–4 mg (3–4 times) in a day. The melting point of Repaglinide is 130–131°C and has mol. wt. of 452.58 [43,44]. It has been proved that repaglinide produces hypoglycemia after oral administration [45]. The Topical preparation of repaglinide may be beneficial to the patient since it reduces adverse effects and avoids the hepatic first-pass metabolism [46,47].

Transdermal patch of atenolol

Atenolol is a beta-adrenergic receptor blocking agent used for the treatment of hypertension [48,49]. The elimination half -life is 6–7 h after oral administration. The absolute bioavailability is approximately 50% due to first -pass metabolism [50,51]. The action of the sympathetic nervous system is blocked by Atenolol. On the basis of that, a transdermal patch has been prepared by using cellulose acetate phthalate, polyvinyl pyrrolidine, and polyethylene glycol [52]. The purpose of the study was to provide the delivery of the drug at a controlled rate across intact skin [53]. It has been reported that administration of conventional tablets of atenolol exhibits fluctuations in the plasma drug level which results in either manifestation of side effects or reduction in drug concentration at the receptor site [54,55]. The researchers developed a transdermal delivery system containing atenolol and hydrochlorothiazide might be a milestone in the combinational therapy of hypertension [56]. The *in vivo* evaluation of formulation (2% Eudragit RS 100, 1%HPMC) has been studied and it shows a better correlation with the *in-vitro* drug release which confirms the achievement of targets of the present study such as controlled prolonged zero-order release, reduced frequency of administration, greater therapeutic effect, overcome the side effects, simplify the treatment regimen and thus may improve patient compliance [57]. A study of transdermal patch of Atenolol has been carried out to develop matrix-based transdermal patches which containing Atenolol. The patches were prepared by solvent casting method.

Transdermal patch of Stavudine

The matrix-type TDD systems of Stavudine have been developed using hydrophilic and hydrophobic polymers for controlled release, showed suitable physicochemical properties. It has been confirmed that Stavudine permeated through the rat abdominal skin and hence could permeate through the human skin [19,58]. Another study revealed that the Transdermal patch of Stavudine has been prepared by using different concentrations of Eudragit RS 100 and Eudragit RL 100. These Prepared patches were found to have smooth and uniform surfaces when they are functional onto the skin [59,60]. It has been proved that the transdermal patch of Stavudine improves the bioavailability of drugs and patient compliance. These patches were characterized by Field Emission Scanning Electron Microscopy. Stavudine has the half -life of 1–1.5 h and bioavailability in the body is 86% due to first-pass metabolism [18].

Transdermal patch of Aceclofenac

ACF inhibited the enzyme COX enzyme. *In vitro* data revealed that the inhibition of Cox-1 and Cox-2 by ACF in whole blood assays, with selectivity for Cox-2 being evident [61]. If ACF is used in patients with ankylosing spondylitis, it reduces the duration of morning stiffness and pain intensity and also improved the spinal mobility [62]. ACF is metabolized to a major metabolite, 4'-hydroxy ACF, and various metabolites including 5-hydroxy ACF, 4'- hydroxydiclofenac, diclofenac, and 5-hydroxydiclofenac [63]. It has been previously described the use of hydroxyl propyl cellulose in transdermal patches and ophthalmic preparations and ethyl cellulose transdermal delivery systems as well as other dosage forms for controlled release of drugs [64-67]. Aceclofenac transdermal patch has been prepared by using a combination of HPMC and MC. A study was conducted using HPMC and MC (50:50) with 30% plasticizer and the results showed that it may be suitable for the development of TDD systems of Aceclofenac [68,69].

Transdermal patch of Zidovudine

Zidovudine (AZT) is a polar molecule. The diffusion of AZT across stratum corneum is poor and below the level to achieve effective therapeutic plasma concentration [70]. It has been previously studied that using terpenes (anethole) along with polyols such as propylene glycol and polyethylene glycol as penetration enhancers could be effective in achieving therapeutic plasma levels for AZT [42,71]. Immediately after intravenous or oral administration, AZT showed excessive plasma level [72]. Therefore, the delivery from a non-oral pathway such as the transdermal route may be helpful in maintaining suitable plasma concentration and also useful in improving bioavailability and patient compliance and in avoiding side effects [73,74]. The benefit of transdermal delivery of AZT has been successfully studied [75,76].

Transdermal patch of ibuprofen

Ibuprofen is employed to ease moderate pain, reduce swelling, control fever, and treat arthritis at higher doses [77,78]. However, along with other NSAIDs, ibuprofen causes (gastritis) which may result in a stomach ulcer or even bleeding [79,80]. A novel TEPI® transdermal patch technology is reported and is exemplified with ibuprofen as the active pharmaceutical ingredient and a new HMPSA cross-linked polymer excipient as a drug reservoir [81,82]. The transdermal patchs of ibuprofen has been evaluated through its organoleptic, weight uniformity, drug content, etc. Ibuprofen is an NSAID drug. It causes gastric irritation when administered orally. The evaluation and formulation of transdermal patch of Ibuprofen have been carried out to prevent this side effect [16].

DISCUSSION

In this review article, we provided valuable information regarding the TDD systems, transdermal patches, and their physicochemical parameters. Furthermore discussed the inflammation, mechanisms of inflammation, studied about the anti-inflammatory drugs, types of inflammation, etc.

CONCLUSION

TDD systems have been effective for painless, efficient, non-toxic, and patient-compliant drug delivery. The development of an efficient means of transdermal administration of NSAIDs may increase local soft tissue and joint concentrations and also reduces the side effects associated with oral administration. Various NSAID drugs may be incorporated for targeting a variety of skin disorders but all NSAIDs cannot be given by this route because of their physicochemical properties which are essential for the transdermal delivery of drugs. Therefore, the potential of this delivery system needs to be explored in the case of NSAIDs. The Transdermal patch of Repaglinide improves the bioavailability of drug and patient compliance. Stavudine has the ability to permeate through the rat abdominal skin and hence could permeate through the human skin. Terpenes (anethole) along with propylene glycol and polyethylene glycol as penetration enhancers could be effective in achieving therapeutic plasma levels for AZT. The Transdermal patch of Atenolol provides the delivery of the drug at a controlled rate across intact skin. Moreover, the transdermal patch has enormous potential to be used not only for the management of inflammatory reactions but also for other conditions requiring transdermal drug release. Moreover, the transdermal patch has enormous potential to be used not only for the management of inflammatory reactions but also for other conditions requiring transdermal drug release.

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AUTHORS' CONTRIBUTIONS

Manuscript framing and the concept has been presented by Deijy Choudhury. Literature search and preparation have been done by Mr.

Ramen Kalita. Reviewing and editing have been done by Mr. Koushik Nandan Dutta.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

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