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TRANSDERMAL PATCHES: A SYNERGISTIC APPROACH OF DRUG DELIVERY FOR NSAIDs

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ABSTRACT

Transdermal drug delivery system has been accepted as potential non-invasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) represents the most commonly used medications for the treatment of pain and inflammation, but numerous well-described side effects can limit their use. Therefore transdermal delivery of NSAIDs has advantages of avoiding hepatic first pass effect, gastric irritation and delivering the drug for extended period of time at a sustained level. The present article gives the brief view on the work been done on various NSAIDs by formulated and delivered as transdermal patches to decrease the side effects associated with the oral delivery. The various NSAIDs included in this article include Ketoprofen, Ibuprofen, Naproxen, Fluribrofen, Diclofenac, Aceclofenac, Ketorolac, Indomethacin, Meloxicam, Nimesulide, Celecoxib, Etoricoxib.

INTRODUCTION: The skin has attracted much attention as an alternative route for administering systemically active drugs. The potential advantages associated with transdermal drug delivery are well documented [1]. Transdermal therapeutic systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system (TDDS) can be designed to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drugs [2].

Non-Steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used class of medications for the treatment of pain and inflammation and represents one of the most common classes of medication used world-wide, with an estimated usage of >30 million per day [3]. NSAIDs are structurally diverse group of compounds known to prevent formation of prostanoids (prostaglandins and thromboxanes) from arachidonic acid through the inhibition of the enzyme cyclo-oxygenase (COX). COX has two isoenzymes: COX-1 is found ubiquitously in the most tissues and produces prostaglandins and thromboxane, while COX-2 is located in certain tissues (brain, blood vessels and so on) and its expression increases during inflammation or fever [4].

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Multiple COX enzymes are responsible for the formation of important biological mediators: such as prostaglandins in response to an inflammatory insult [5].

Conventional NSAIDs inhibit both forms of COX. The assumption that anti-inflammatory efficacy is due to inhibition of COX-2 whilst toxic side effects are mainly caused by inhibition of COX-1 has led to the development of selective COX-2 inhibitors [6].

To eliminate the side effects associated with the oral administration of NSAIDs, non oral routes may be preferred. Indeed, transdermal drug delivery of NSAIDs is feasible in recent years. As expected, the system appears to minimize gastrointestinal side effects and hepatic first pass effect. Furthermore, the controlled and sustained release of the active ingredients may be achieved with an enhanced patient compliance [7].

Non Selective COX Inhibitor: This class is also known as traditional NSAIDs. The examples of drugs included in this class are: Ketoprofen, Ibuprofen, Naproxen, Fluribrofen, Diclofenac, Aceclofenac, Ketorolac, Indomethacin etc.

1. **Ketoprofen:** Ketoprofen is a propionic acid derivative that inhibits both cyclooxygenase (nonselectively) and lipoxygenase [8]. The mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs), to which Ketoprofen belongs, is based on their cyclo-oxygenase (COX) inhibiting action, concerning both subtype COX-1 constitutive isoform and COX-2 inducible isoform. Ketoprofen administration may be carried out by oral and parenteral routes as well as by topical application, which includes transdermal patch use [9].

   Adachi H *et al.,* developed a new formulation of the ketoprofen patch obtained by the so called DermaLight Technology. In this technique, the active principle is dissolved in oil components and dispersed inside an anhydrous polymeric matrix made up of styrene-isoprene-styrene (SIS), which is an elastic and flexible material that provides a gentle adhesion to the skin, maintains an elevated ketoprofen concentration and induces a strong thrust that favours the crossing of the skin by the drug; in addition, the patch is fit to be applied to the various areas of the body, including the joints. The results indicated that patch adhesiveness reduces skin irritation due to multiple applications and to long-term use, as the DermaLight Technology minimises keratinocytes exfoliation. In pharmacokinetic studies carried out on pigs ketoprofen has been demonstrated to reach deep tissues, where the drug was detected in much higher concentrations, with respect to plasma levels, 12 hours following its application.

   Experimental studies carried out on rats have shown that ketoprofen patch significantly reduces the edema induced by chronic inflammation. The ulcerogenic effect of ketoprofen patch is then compared with that shown by oral administration of the drug. UD50 values of ketoprofen patch were 49.9 mg/kg and 48.9 mg/kg for the stomach and the small intestine, respectively, whereas UD50 values of oral ketoprofen were 3.6 mg/kg and 3.7 mg/kg, respectively. So ketoprofen patch can be used as both a good alternative and a safe modality of administration, with special reference to patients who are prone to gastrointestinal disorders [9].

   Shashikant D. Barhate *et al*., developed a transdermal delivery system of ketoprofen. The transdermal patches of ketoprofen were prepared by mercury substrate method using polymer Eudragit RS100, Eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer. The prepared patches will evaluated for thickness, folding endurance, tensile strength, drug contain uniformity, *in-vitro* permeation study.

   Drug polymer interactions determine by FTIR and standard calibration curve of ketoprofen were determine by using UV estimation. *In vitro* release study was performed by using Franz-diffusion cell. Patches prepared with HPMC with enhancer propylene glycol showed higher % moisture transmission. The formulated transdermal patch by using EudragitRS100, EudragitRL100, HPMC K100M, HPMC E5 and HPMC K4M showed good physical properties.

It was observed that the formulation containing HPMC E5 showed ideal zero-order release kinetics [10].

2. **Ibuprofen**: Ibuprofen is a simple derivative of phenylpropionic acid. In doses of about 2400 mg daily, ibuprofen is equivalent to 4 g of aspirin in anti-inflammatory effect [11]. Ibuprofen is a NSAID used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea acts mainly by inhibition of COX-1 and COX-2.

   Thushara Bindu D *et al*., prepared transdermal patch of ibuprofen by using gelatin, sodium benzoate and glycerine as main ingredients. In order to increase its permeability, permeation enhancers like olive oil, coconut oil and sun flower oil were used and the patches were characterized by evaluating physicochemical parameters like thickness, weight variation, folding endurance, drug content, breaking strength and ex vivo release study. From this study, it was concluded that olive oil is the better permeation enhancer for Ibuprofen transdermal patch [12].

3. **Naproxen:** Naproxen is a naphthylpropionic acid derivative. It is the only NSAID presently marketed as a single enantiomer, and it is a nonselective COX inhibitor. Naproxen is effective for the usual rheumatologic indications [11]. It is particularly potent in inhibiting leucocyte migration [8].

   Argemi A *et al*., prepared and characterized transdermal patches impregnated with naproxen. A mixture of ethylene vinyl acetate and Eudragit E100 (80:20, w/w) is used as a polymeric matrix to obtain a thin membrane to be impregnated. Drug impregnation is carried out under pressurized CO_2 as a processing medium according to a two-step procedure. The patch is first soaked at 1000 psi and 22°C for 2 h, and then foamed as a result of the rapid release of CO_2 pressure in order to increase the porosity of the surface.

   Subsequently, the naproxen solution is placed in contact with the membrane and then soaked in CO_2 at 450 psi and 37°C for 2.5 h to enhance the mass transfer of drug into the polymer matrix.

   The naproxen content and distribution of the resulting samples are characterized by liquid chromatography, microscopy, and calorimetry. Patches synthesized in this way are loaded with about 1% naproxen. The drug release and diffusion process through a membrane have been studied chromatographically using a Franz diffusion cell. Results have shown that a sustained delivery of naproxen for more than 24 h is obtained [13].

   G Parthasarathy *et al*., developed transdermal drug delivery system of Naproxen with Ethylcellulose and Hydroxy propyl methyl cellulose polymer in various concentrations. Tramsdermal films were fabricated by matrix technique with various polymer proportions using dibutylphthalate as plasticizer. These transdermal drug patches were characterized for their thickness, tensile strength, content uniformity, *in-vitro* release. The release profiles were found to be varied with various concentrations of Ethylcellulose Polymer. The sample of patches prepared with 2:8 and 8:2 ratios of Ethyl cellulose and Hydroxy propyl methyl cellulose shows highest and lowest *in-vitro* release of Naproxen respectively [14].

4. **Flurbiprofen:** Flurbiprofen is a potent non steroidal anti-inflammatory, analgesic and antipyretic drug [15]. It is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs. Its *(S)*(–) enantiomer inhibits COX nonselectively, but it has been shown in rat tissue to also affect TNF-α and nitric oxide synthesis. Hepatic metabolism is extensive; its *(R)*(+) and *(S)* (–) enantiomers are metabolized differently, and it does not undergo chiral conversion.[11].

   Charoo NA *et al*., fabricated reservoir type of transdermal patch using flurbiprofen viscous system, ethylene vinyl acetate membrane, and backing film. The flux of flurbiprofen through ethylene vinyl acetate microporous membrane was evaluated. The maximum flux achieved by Isopropyl alcohol (IPA): Propylene glycol (PG) (70:30% v/v) solvent mixture was further increased by lemon oil. Histological investigations were done on rat skin samples treated with solvent systems with or without penetration enhancer for 24 hr. No skin irritation was seen.

Lemon oil produced more pronounced change in stratum corneum and the epidermis as compared with the control groups. The pharmacokinetics of flurbiprofen in albino rats following application of a transdermal patch for 24 hr was evaluated. The maximum plasma concentration (C_{max}) and AUC($_{0\text{-}alpha}$) of the patch formulation was 1.7 and 1.6 times, increased respectively as compared with the control patch formulation. Anti-inflammatory effect in the Carrageenan-induced paw edema in rat was significantly higher than the control patch formulation [16].

5. **Diclofenac:** Diclofenac is an aryl-acetic acid derivatives, it is an analgesic-antipyretic-anti-inflammatory drug similar in efficacy to naproxen. It inhibits prostaglandin synthesis and is somewhat COX-2 selective. It is well absorbed orally, 99% protein bound, metabolized and excreted in urine and bile. The plasma $t_{1/2}$ is ~2 hours. Oral administration of diclofenac is therefore poorly tolerated and causes stomach ulceration. It would be preferable to achieve therapeutic drug concentrations in the target tissue while simultaneously keeping the systemic and gastrointestinal agent concentrations as low as possible.

   Obviously, such a goal can only be achieved by delivering diclofenac into the body via a route other than the mouth. For this reason, percutaneous administration of diclofenac has been studied as a way to minimize these gastrointestinal side effects [17].

   Rajan Rajabalaya *et al.,* designed suitable matrix patch formulations of ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) with either dibutyl phthalate (DBP) or propylene glycol (PG) as the plasticizer by solvent casting method for long-acting permeation of diclofenac potassium (DP). The *in vitro* release and skin permeation studies were carried out in a modified Keshary–chien diffusion cell and the rates were determined by UV spectroscopy. The average drug content, thickness, tensile strength, moisture content and water absorption capacity of the matrix patches were also determined.

   It was found that most of the release profiles followed Fickian diffusion except for two formulations with DBP following Higuchi release. It was also observed that the permeation profiles exhibited concentration dependent first-order kinetics [18].

   Priyanka Arora *et al*., prepared matrix-type transdermal patches containing diclofenac diethylamine using different ratios of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique. The drug matrix film of PVP and EC was casted on a polyvinylalcohol backing membrane. All the prepared formulations were subjected to physical studies (moisture content, moisture uptake, and flatness), *in vitro* release studies and *in vitro* skin permeation studies.

   In vitro permeation studies were performed across cadaver skin using a modified diffusion cell. Variations in drug release profiles among the formulations studied were observed. Based on a physicochemical and in vitro skin permeation study, formulation PA4 (PVP/EC, 1:2) and PA5 (PVP/EC, 1:5) were chosen for further *in vivo* experiments. The anti-inflammatory effect and a sustaining action of diclofenac diethylamine from the two transdermal patches selected were studied by inducing paw edema in rats with 1% w/v carrageenan solution.

   It was observed that formulation PA4 produced 100% inhibition of paw edema in rats while in case of formulation PA5 19.23% inhibition of paw edema was obtained 12hr after the carrageenan injection. The efficacy of transdermal patches was also compared with the marketed Voveran gel.

   Hence, it can be reasonably concluded that diclofenac diethylamine can be formulated into the transdermal matrix type patches to sustain its release characteristics and the polymeric composition (PVP/EC, 1:2) was found to be the best choice for manufacturing transdermal patches of diclofenac diethylamine among the formulations studied [19].

Zhonggui He *et al*., prepared and evaluated monolithic drug-in-adhesive type patches of diclofenac diethanolamine (DFD) containing penetration enhancers. The patches containing 2% DFD were prepared using Eudragit E100 and polyvinylpyrrolidone (PVP) as the adhesive polymer by the solvent evaporation technique. The effects of different pressure-sensitive adhesive and various permeation enhancers (Tween-80, propylene glycol, Azone, N-methyl-2-pyrrolidone, menthol) on the *vitro* percutaneous absorption of diclofenac across rat skin were evaluated using a 2-chamber diffusion cell system.

Four formulations were developed which differed in the ratio of the matrix forming polymers, Eudragit E100 and PVP, *i.e.* 7: 3, 6: 4, 4: 6 and 3: 7. A patch consisting of Eudragit E100/PVP (6: 4) showed a much higher release rate and skin permeation flux than Eudragit E100/PVP (7:3), Eudragit E100/PVP (3:7) and Eudragit E100/PVP (4: 6) and flux value of the patch containing N-methyl-2-pyrrolidone (NMP) was higher than four the other penetration enhancers tested. Based on the release profile and *in vitro* skin permeation studies, the formulation Eudragit E100/PVP (6:4) containing NMP was found to be the best choice for transdermal patches of DFD in the formulation studies carried out [20].

C. Mallikarjuna Setty *et al*., developed ethylcellulose transdermal patches for diclofenac diethylamine (DDA) using chemical penetration enhancers developed. Effect of drug loading and penetration enhancers on the in vitro permeation of drug through cellophane membrane and rat skin was investigated. Incorporation of penetration enhancers enhanced the moisture content, moisture uptake capacity and permeation of diclofenac diethylamine across skin barriers.

Among the penetration enhancers used, propylene glycol found to be most effective. The anti-inflammatory effect of formulation with penetration enhancer was more than that without penetration enhancer. Stability studies did not show any degradation of the drug.

Therefore, stable and effective diclofenac diethylamine transdermal patches can be prepared using chemical penetration enhancers [21].

6. **Aceclofenac:** Aceclofenac is poorly water soluble, NSAID, which acts specifically on inflammatory sites and thereby decreases the inflammation. It is highly effective as an anti-inflammatory drug for various inflammatory conditions like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Although aceclofenac has a strong therapeutic effects, when taken orally for prolonged period. It possesses lower molecular weight (354.1) and relatively short half life (4-43 h) in plasma and has the potential to be delivered by transdermal route [22].

D.V. Gowda *et al*., formulated transdermal film loaded with Aceclofenac (ACF) by solution casting method using chemically modified locust bean gum (MLBG) and sodium alginate (SA) in various proportions and examines the influences of various process parameters like drug: polymer ratio, concentration of plasticizer (glycerol) and permeation enhancer (menthol) on physicochemical properties of drug loaded transdermal film and drug release potential. *An in-vitro* skin permeation study of optimized formulation was studied.

Carrageenan induced rat paw edema model was used to investigate their *in vivo* performance. The drug content uniformity of the prepared films lies in the range of 1.90 to1.95 mg/cm^2. Increased ratio of MLBG and decreased ratio of SA showed decreased tensile strength with increased % elongation. The thickness of the films varied from 0.29 to 0.38 mm due to increased MLGB and decreased ratio of SA.

Folding endurance decreases as the MLGB concentration increases with decreased SA ratio. ACF was found to be compatible and stable with the prepared formulation as confirmed by Fourier transform infrared (FTIR) and Differential Scanning Calorimetry (DSC) studies. *In-vitro* skin permeation studies showed a controlled release for 24h. Skin irritation test reveals no signs of erythema, edema or ulceration.

The study results suggest that polymer based prepared transdermal films are potential vehicle to achieve controlled transdermal delivery of ACF for effective therapy and showed good skin tolerability [23].

Rakesh P. Patel *et al*., developed a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Aceclofenac.

The physicochemical compatibility of the drug and the polymers studied by differential scanning calorimetry and infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best *in-vitro* skin permeation through rat skin (Wistar albino rat) as compared to all other formulations.

The results followed the release profile of Aceclofenac followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation F9 (r^2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

Formulation F9 showed highest flux among all the formulations and 1.369 fold enhancements in drug permeation. These results indicate that the formulation containing 15 % of oleic acid with 10 % Isopropyl myristate give better penetration of Aceclofenac through rat skin [24].

Shankar M.S. *et al*., prepared matrix-type transdermal patches containing Aceclofenac using different ratios of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique using 10%w/w of dibutyl phthalate incorporated as plasticizer. The drug matrix film of PVP and EC was casted on a polyvinylalcohol backing membrane that was previously dried at 60^0C for 6 hrs. All the prepared formulations were subjected to physical studies (moisture content, moisture uptake, Tensile strength, flatness and Drug content determination), *in vitro* release studies and in vitro skin permeation studies.

The physiochemical compatibility of the drug and the polymers studied by infrared spectroscopy suggested absence of any incompatibility. In vitro permeation studies were performed across cadaver skin using a Franz diffusion cell. Variations in drug release profiles among the formulations studied were observed. Based on a physicochemical and in vitro skin permeation study, formulation F1 (PVP/EC, 5:1) and F5 (PVP/EC, 1:5) were chosen for further in vivo experiments. The anti-inflammatory effect and a sustaining action of Aceclofenac from the two transdermal patches selected were studied by inducing paw edema in rats with 1% w/v carrageenan solution.

When the patches were applied half an hour before the sub plantar injection of carrageenan in the hind paw of male Wistar rats, it was observed that formulation F1 produced 91.04% inhibition of paw edema in rats 10hrs after carrageenan insult, whereas in the case of formulation F5, the value became 43.34% at 10 hrs after the carrageenan insult. Hence, it can be reasonably concluded that Aceclofenac can be formulated into the transdermal matrix type patches to sustain its release characteristics [25].

7. **Ketorolac:** Ketorolac is a pyrrolo-pyrrole derivative, with potent analgesic and modest anti-inflammatory activity. Like other NSAIDs, it inhibits prostaglandin synthesis and relieves pain by a peripheral mechanism [8]. Although, oral bioavailability of ketorolac was reported to be 90% with very low hepatic first-pass elimination, the biological half-life of 4 to 6 hours requires frequent

administration to maintain the therapeutic effect. The long-term use of currently available dosage forms of ketorolac may result in gastrointestinal ulceration and acute renal failure [26].

Amrish C *et al*., fabricated reservoir type transdermal patch and the core was filled with gel system of a non ionic polymer HPMC (hydroxypropyl methyl cellulose) formulated in PBS (phosphate buffer saline) solution of pH of 5.4 along with isopropyl alcohol at 25% w/w concentration. Various permeation enhancers viz. dimethyl sulphoxide, d-limonene, eucalyptus oil and transcutol (diethylene glycol monoethyl ether) were incorporated into the gel system. Permeation enhancement of ketorolac with different enhancers followed the order eucalyptus oil> transcutol> DMSO> d-limonene.

Cyclic terpene containing eucalyptus oil was found to be the most promising chemical permeation enhancer for transdermal delivery of ketorolac. The increase in concentration of eucalyptus oil further enhanced drug permeation with maximum flux being achieved at 10% w/w of 66.38microg/cm^2/h. Further enhancement of permeation rate of ketorolac across skin was attained by application of abrading gel containing crushed apricot seed onto the skin. There was 5.16 times enhancement and flux of 93.10microg/cm^2/h was attained. A reservoir type transdermal patch for delivery of ketorolac thus appears to be feasible of delivering ketorolac across skin [27].

Satyanarayan Pattnaik *et al*., developed a suitable transdermal matrix patch of ketorolac tromethamine with different proportions of polyvinyl pyrrolidone (PVP) and ethyl cellulose (EC) using a D-optimal mixture design. The prepared transdermal patches were subjected to different physicochemical evaluation. The surface topography of the patches was examined by scanning electron microscopy (SEM). The drug-polymer interaction studies were performed using Fourier transform infrared spectroscopic (FTIR) technique. A correlation between *in-vitro* drug-release and *in-vitro* skin permeation was established and the criterion of desirability was employed to optimize the formulation.

The results of the physicochemical characterization and in-vitro permeation of the prepared patches were promising to formulate transdermal patches with PVP/EC combinations [28].

Chandra A *et al.,* formulated reservoir type transdermal patch in which the core of the transdermal patch was filled with the hydrogel of a nonionic polymer, methocel K_{15} M (hydroxyl propyl methylcellulose, HPMC) formulated at an optimized pH of 5.4. Enhanced *in vitro* permeation was achieved after the incorporation of the alcohols. Higher enhancement was produced by short-chain alcohols like ethanol and isopropyl alcohol (IPA). Propylene glycol (PG) along with other alcohols, viz. n-propanol, n-butanol, and n-pentanol, lagged behind.

An exponential rise in permeation was observed in flux with an increase in the concentration of IPA. At 25%w/w IPA concentration, the observed ketorolac flux was 18.04mg/cm^2/h. Terpene containing eucalyptus oil was studied to determine its permeation enhancement capability. The increase in the concentration of eucalyptus oil enhanced the drug permeation and a maximum flux of 66.38 and 90.56mg/cm^2/h was achieved at 10 and 15%w/w concentrations. The anti-inflammatory potential of the transdermal formulation was evaluated on a carrageenan-induced paw edema model, with 41.67% inhibition at 6 h. The skin irritation potential was evaluated by the Drazie test and the formulations prepared were found to be safe. The reservoir-type transdermal patch for the delivery of ketorolac appeared to be feasible for delivering ketorolac across the skin [29].

Beny Baby *et al.,* formulated and evaluated the membrane permeation controlled type transdermal patches of Ketorolac tromethamine, the patches were prepared by using different polymers such as PVP, hydroxyl propyl methyl cellulose, methyl cellulose, ethyl cellulose in different proportions and combinations. *In-vitro* dissolution studies were carried out till the complete exhaustion of the loaded drug from the membrane. Order of release and mechanism was evaluated by graphical treatment according to Higuchi's equation and it has shown the drug

release was diffusion mediated. In this study HPMC-2% and MC-3% was found best because of its consistent release rate, extent of drug release, reduced frequency of administration, avoids the first pass effect. The formulation has achieved the objectives of extended release, reduced frequency administration, avoids the first pass effect and thus may improve the patient compliance [30].

G. Fetih *et al*., developed suitable film formulations of ketorolac tromethamine (KT) for transdermal use by using polyvinyl alcohol (PVA), sodium carboxymethylcellulose (NaCMC), and chitosan were used as film-forming polymers, and investigated the effect of film composition and permeation enhancers on the in-vitro release and skin permeation of the drug. The adhesive hydrophilic polymers plastoid® E35L (PL E35) and polyvinyl pyrrolidone (PVP) were added to improve bioadhesion. The permeation enhancers used were oleyl alcohol (OA), sodium glycocholate (NaGC) and propylene glycol (PG).

Formulated films were characterized by measuring their mean thickness, mass, drug content, folding endurance and bioadhesion. In-vitro release was studied using the USP XXIII rotating paddle method and *in-vitro* permeation across hairless rat skin was studied using an *in-vitro* diffusion cell. Addition of PVP enhanced the drug release and permeation especially in case of chitosan, while Plastoid® E35L improved permeation only. Skin permeation of the drug was greatly improved by the addition of permeation enhancers, the rank of their effectiveness was: sodium glycocholate (Na GC) > oleyl alcohol (OA) > propylene glycol (PG). The results obtained showed that these polymeric films can be a promising therapeutic system for the transdermal delivery of ketorolac.[31]

8. **Indomethacin:** It is a potent anti-inflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory or tissue injury related pain. It is highly potent inhibitor of prostaglandin synthesis and suppresses neutrophil motility. Plasma t1/2 is 2-5 hours [8]. The administration of indomethacin via the dermal route has been adopted to bypass the disadvantages of the oral route and maintain relatively consistent plasma levels for long-term therapy. Indomethacin appears to be a good transdermal candidate, and different approaches, such as using prodrugs, chemical enhancers, iontophoresis and ultrasound have been developed to improve indomethacin skin permeation [32].

Liang Fang *et al*., formulated drug-in-adhesive type patch using MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive. A variety of permeation enhancers (i.e. azone, L-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid) were also used in the formulation. The enhancing effects of the permeation enhancers were evaluated using two-chamber side-by-side diffusion cells containing excised rat skin. Differential scanning calorimetry was used to evaluate the compatibility between indomethacin and MASCOS 10.

Tack, shear strength and peel strength were measured to estimate the adhesion of the patch because the adhesive is critical for the safety, efficacy and quality of the product. The drug content and drug release rate of the patch are also essential standards in industrial process, so the work was complicated. It was notable that the presence of IPM, oleic acid and Tween 80 did not increase indomethacin permeation from the transdermal patches compared with the transdermal patches containing azone and L-menthol ($P > 0.05$). 5% azone and 5% L-menthol were the permeation enhancers of choice for the percutaneous absorption of indomethacin. The adhesion properties of the patches were very satisfactory. Also, the prepared patches showed good uniformity with regard to drug content and drug release.[32]

Preferential COX-2 Inhibitor: This class of NSAIDs are relatively weak inhibitors of prostaglandin synthesis and there is some evidence to indicate relative COX-2 selectivity. Antiinflammatory action may be exerted by other mechanism as well, e.g. reduced generation of superoxide by neutrophils, inhibition of platelet activating factor (PAF) synthesis and TNFα release, free radical scavenging, inhibition of metalloproteinase

activity in cartilages. The example of drugs included in this class is meloxicam, nimesulide etc.[8]

1. **Meloxicam:** Meloxicam is a potent non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class of oxicam derivatives. Its mode of action is via preferential inhibition of cyclo-oxygenase-2 (COX-2) activity and prostaglandin synthesis. Meloxicam has proven efficacy in treating rheumatoid arthritis, osteoarthritis, and many other joint diseases [33].

   Ah YC *et al*., designed a monolithic drug-in-adhesive (MDIA) type patch containing meloxicam (MX) with an acrylic adhesive, a solubility modulator increasing MX solubility, and enhancers. In this research, solubility modulators to increase solubility of MX and acrylic adhesives and skin permeation enhancers were investigated through solubility tests, in vitro skin permeation tests, and stability tests. Consequently, the composition of sodium methoxide (SM), an acrylic adhesive containing poly(vinyl pyrrolidone) blocks (MAS683), polyoxyethylene cetylether (BC-2), and diisopropanolamine (DIPA) made it possible for MX to be contained in an adhesive layer at a concentration of as much as 15 wt% without MX crystal and with high skin permeation over 400 microG/cm^2.

   Finally, the patch formulation containing MX (MX-patch) selected through our in vitro study was characterized by *in vivo* using an animal study to acquire pharmacokinetic (PK) parameters and to confirm the anti-inflammatory efficacy of MX-patch. In the animal study, MX-patch was compared with a commercially available piroxicam patch (PX-patch).

   The amount of MX delivered from MX-patch to the skin surface was believed to be higher than the amount of MX diffused from the skin tissue to circulatory system because the plasma concentration of MX continuously increased up to 32 h, the end time of PK study, although the patch samples were detached at 24 h. PX-patch produced a C_{max} at 8 h. MX-patch showed better significant efficacy than PX-patch in adjuvant arthritis model [34].

   Manish Kumar *et al*., fabricated matrix diffusion controlled transdermal drug delivery system of meloxicam by solvent evaporation technique using various concentration ratios of polymer (pectin). These transdermal drug delivery systems were characterized for their thickness, weight variation, folding endurance, swelling index, content uniformity, compatibility, *in-vitro* release and skin irritation studies of the drug from the polymeric matrix.

   Meloxicam was found to be compatible with pectin as revealed by Fourier Transform Infrared Spectroscopy (FTIR) studies and showed satisfactory physiochemical characteristics. *In-vitro* release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffer as receptor medium and it showed controlled release of drug. Thus the prepared transdermal films can be used to achieve controlled release and improved bioavailability of meloxicam [35].

2. **Nimesulide:** It is an effective non-steroidal drug used as anti-inflammatory, analgesic and antipyretic. It is used in the treatment of osteoarthritis and rheumatoid arthritis. Though rapidly absorbed following oral administration, it undergoes significant first-pass metabolism. Its half-life is about 1.8 to 4.73 h [37].

   Rajagopal K *et al*., formulated and evaluated matrix type transdermal patches of nimesulide by using different polymers alone or in combination, dibutyl phthalate as the plasticizer and aluminium foil as the backing membrane. *In-vitro* release studies of the prepared formulations were performed by keshary-chien diffusion cell through cellophane membrane and excised mice skin in phosphate buffer solution (pH7.4).

   Both the studies showed that (2:2) hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) combination may be the suitable polymer combination for development of transdermal drug delivery system (TDDS) of Nimesulide. The patches were further evaluated for physicochemical characteristics and skin-irritancy test [36].

Putta Rajesh Kumar *et al*., prepared monolithic transdermal films of Nimesulide (NIM) were to avoid hepatic first pass effect by using hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) alone and in combination with co-polymer poly vinyl pyrollidone (PVP) by solvent casting method. Dibutyl phthalate (DBP) was used as plasticizer. d-limonene and oleic acid were used as permeation enhancers. The formulations were evaluated for physical appearance, thickness uniformity, weight uniformity, drug content uniformity and water vapour transmission rate. In further study the co-polymer and permeation enhancers effect on in vitro drug release from the films was studied by using Keshary-Chein diffusion cell.

Permeation parameters like diffusion rate, permeability coefficient, flux, enhancement ratio and permeability rate were determined. The films containing PVP showed more permeation than films with HPMC and EC alone. The monolithic film made up of HPMC and PVP with 10%w/w d-limonene showed better *in vitro* permeation through rat skin. *In vitro* permeation of NIM from the films was diffusion controlled and followed zero order kinetics. The transdermal film showed better permeation was subjected for *in vivo* studies and it showed anti-inflammatory and analgesic activity statistically significant at $P < 0.05$. It was concluded that the above transdermal drug delivery system could be useful to treat chronic pain and inflammation in arthritis [37].

Selective COX-2 Inhibitors: In the 1990s, a new class of drugs collectively known as selective inhibitors of cyclooxygenase 2 (COX-2) was developed for the treatment of pain and inflammation. Selective COX-2 inhibitors (coxibs) were designed to be at least as efficacious as the common non-steroidal anti-inflammatory drugs (NSAIDs), but to lack one of their major side effects, gastrointestinal (GI) bleeding [38].

The premise that COX-1 performs cellular "housekeeping" functions for normal physiologic activity and is the predominant isoform expressed in platelets and the GI tract, whereas COX-2 acts at inflammatory sites, led to the development of COX-2 selective inhibitors [3].

Currently 3 selective COX-2 inhibitors (also called coxibs) celecoxib, etoricoxib, parecoxib are available in India [8].

1. **Celecoxib:** Celecoxib (CXB), a selective cyclo-oxygenase-2 (COX-2) inhibitor, has been recommended orally for the treatment of arthritis and osteoarthritis. The COX-2 selectivity of celecoxib is modest (6-20 fold). The t1/2 is ~10 hours and is 97% plasma protein bound. Long-term oral administration of CXB causes serious gastrointestinal side effects. Therefore, an improved CXB formulation with a high degree of permeation could be useful in the treatment of locally inflamed skin and inflammatory and painful states of the body [8, 39].

   S Jayaprakash *et al*., prepared transdermal patches of celecoxib were by using different polymers such as hydroxyl-propylmethylcellulose (HPMC), methylcellulose (MC), Polyvinylpyrolidone (PVP). The *in-vitro* releases of the drug from the formulations were studied using commercial semi permeable membrane. The prepared formulation were subjected to various physicochemical evaluation test, *in-vitro* dissolution studies, kinetics studies shows diffusion might be one of the prominent mechanism influencing the drug release. Peppas plot was drawn, which confirmed that the diffusion mechanism involved in the drug release was of non fickian diffusion type. ex-vivo diffusion studies by using rat skin, guinea pig skin and pig ear skin and finally in-vivo evaluation studies (the patch F4 HPMC 0.75%, PVP 0.25%) were carried out by using rabbits [40].

   Alam MI *et al*., developed low-dose, matrix-type transdermal patches containing celecoxib for the treatment of osteoarthritis. The patches were designed to be used over a period of 24 h. Different ratios of ethyl cellulose/polyvinyl pyrrollidone (EC/PVP) were used for the development of the system. All of the prepared patches were subjected to physicochemical evaluation, in vitro drug release, permeation, and anti-inflammatory studies (*in vivo*). The release rates and flux increased linearly when an increase in the fraction of PVP was mixed with the formulations.

In vitro studies showed enhanced performance in the presence of an enhancer (5% v/v oleic acid). The cumulative amount of drug permeated was found to be proportional to the square root of time (following the Higuchi equation). The anti-inflammatory effect (*in vivo*) and sustained action were studied by a carrageenan-induced (1% w/v) rat hind paw edema method.

The selected formulation (EC/PVP, 2:3) produced 100% inhibition of paw edema in rats up to 6 h after receiving the carrageenan injection. The inhibition was 94.42%, 89.77%, and 86.44% after 8, 12 and 24 h, respectively. From this study it can be concluded that celecoxib can be formulated into a patch for transdermal delivery. Therefore, celecoxib can be recommended for further pharmacokinetic and pharmacodynamic studies in suitable animal models [41].

Gilhotra Ritu Mehra *et al*., prepared matrix type transdermal drug delivery system of celecoxib by the film casting method and characterised by physicochemical, in vitro by drug release studies, skin permeation studies and *in vivo* studies. Eight formulations were developed, which differed in the ratio of matrix forming polymers (PVA and HPMC) individually or in combination. All the eight formulations carried 2% m/m of celecoxib, eucalyptus oil or isopropyl alcohol as a permeation enhancer (10% v/v), plasticiser (20% w/w of polymer). Cumulative amounts of the drug released in 12 h from the eight formulations were ranged from 96.40±0.04 to 99.68±0.05 %.

In vitro drug release was found to follow zero order kinetics and Higuchi kinetics. The cumulative amounts of the permeated drug for developed formulation ranged from 87.18±0.09 to 96.01±0.05 %. On the basis of in vitro drug release and skin permeation study, formulation F1 was found to be better than the other seven formulations and it was selected to *in vivo* studies.

Paw edema study was done in Wistar rat, Maximum percentage inhibition was observed for oral and transdermal application as 59.14% and 89.96%, respectively. An inhibition in paw edema volume of 31.95% and 39.30% was observed on oral and transdermal application of drug in adjuvant arthritis, chronic model in Wistar rat, as well [42].

2. **Etoricoxib:** This newer COX-2 inhibitor has the highest COX-2 selectivity. It is suitable for once a day treatment of osteo/rheumatoid/acute gouty arthritis, dysmenorrhoea, acute dental surgery pain and similar conditions. The t1/2 is ~24 hours [8].

   B. K. Sridhar *et al*., prepared drug free polymeric films of chitosan, chemically modified chitosan and chitosan/hydroxypropylmethylcellulose blend and films were evaluated for various physicochemical characters. Chitosan has been chemically modified by treating with two different aldehydes like acetaldehyde and propionaldehyde to form Schiff's bases. Schiff's bases of chitosan with acetaldehyde and propionaldehyde were named as polymer A and polymer B, respectively.

   Fourier Transform Infra Red (FTIR) spectral data have confirmed the reaction carried out on chitosan. Further, the films were incorporated with anti-inflammatory drug, etoricoxib using glycerol as plasticizer. The drug loaded films were cross-linked with sodium citrate and studied for permeation characteristics across dialysis membrane and rat skin. All the films were evaluated for bursting strength, swelling index, moisture uptake, thickness uniformity, drug content uniformity, tensile strength, percent elongation at break, percent flatness, water vapour transmission rate and *in vitro* drug permeation study [43].

CONCLUSION: Oral non steroidal ant-inflammatory drugs (NSAIDs) are effective pharmacotherapy for a wide variety of painful, inflammatory disorders. Development of an efficient means of transdermal administration of NSAIDs could increase local soft tissue and joint concentrations while reducing side effects associated with oral administration.

All NSAIDs cannot be given by this route because the drug should possess certain physicochemical properties which are prerequisite for the transdermal delivery of drugs. Thus, the potential of this delivery system need to be explored in case of NSAIDs.

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