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PHYSICAL METHODS FOR ENHANCEMENT OF TRANSDERMAL DRUG DELIVERY IN PAIN MANAGEMENT

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ABSTRACT: Pain is the major symptom associated with many diseases and disorders. Whether acute or chronic, pain causes much distress to the patient and can be debilitating in many cases. The quest for safe and effective pain management has driven the research efforts of the scientists for several decades. These ongoing efforts to come up with optimum therapeutic systems to deliver pain relief medication have propelled the researchers to explore different routes of drug administration, along with different means to facilitate drug delivery via a particular route. In view of the limitations of conventional methods to provide pain relief, as well as, the adverse effects associated with the traditional routes of drug delivery, the transdermal route of drug delivery has drawn the interest of scientists world over, owing to which a number of therapeutic breakthroughs have been achieved. In the past few decades, many novel drug delivery systems have been developed to deliver analgesics (NSAIDs and opioids) and anesthetics by means of transdermal therapy. The results obtained from the various studies attempted by the researchers suggest that the transdermal drug delivery systems are capable of causing significant reduction in pain levels, without causing gastrointestinal toxicity. As such, these systems can not only be made a part of the disease management strategy but also physical or chemical means. While the former involves the use of techniques like iontophoresis, electrophoresis, ultrasound, needleless injections and microneedles, the latter encompasses the use of chemical penetration enhancers to facilitate drug delivery across the skin. The present review attempts to furnish an overview of the physical techniques explored to deliver analgesics transdermally and the studies conducted in this domain.

INTRODUCTION: Ever since the human life came upon earth, man has been looking to find out better and better alternatives to alleviate pain, which is a symptom common to most of the ailments affecting human beings.

According to International Association for the study of pain (1979), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain signifies real or potential tissue damage and life threat and, provides, powerful incentive to understand what is happening to the individual [1].

Psychological factors have great impact on pain perception. Pain perception is influenced both by sensory qualities and the emotional impact [2]. Although, a great number of pain relieving drugs, both herbal and synthetic, are available but the

researchers are still posed with the challenge to come up with drug delivery system that gives the maximum therapeutic effect of the drug, without exposing the patient to the adverse effects. In addition to these, the delivery system should be so designed that it allows the release of the drug to be tailored to the needs of the patient i.e. immediate release or prolonged release. Depending upon the disease or disorder afflicting the patient, the pain may vary in its nature, intensity and duration. Pain is classified as follows:

Neuropathic and nociceptive pain:
Neuropathic pain results due to abdominal processing of sensory input by peripheral or central nervous system. Nociceptive pain is either somatic (i.e. arising from skin, bone, joint, muscle or connective tissue) or visceral (arising from internal organs such as large intestine or pancreas) [3].

Acute and chronic pain:
Pain may also be classified as acute and chronic pain. Comparison of both acute and chronic pain is shown in **Table 1**.

TABLE 1: COMPARISON OF ACUTE PAIN AND CHRONIC PAIN [4]

Acute Pain	Chronic Pain
Sudden onset	Sudden or gradual onset
Temporary (up to 3 months)	Persistent
	Pain can be constant or come and go
Pain lessens over time	Pain worsens over time
Stress response may be present (i.e. increased heart rate, blood pressure and breathing rate)	Stress response is often absent
Nature's warning signal	Considered a diseased state; serves no useful purpose
Topical patches in use are NSAIDs and fentanyl patches.	Localized delivery may be useful. Patches which can be use are topical capsacicin and lidocaine patches.

Pain is characterized by certain clinical features, enumerated below:

Inflammatory- Pain, color change, temperature change, limitation of movement, exacerbation by exercise, edema.

Neurological- Allodynia, involuntary muscles spasms, hyperpathia, pareisis, pseudoparesis, incoordination tremor [5].

Furthermore, pain receptors may be grouped as whether they respond to mechanical, thermal or chemical stimuli or to a wide variety of irritating chemicals, such as bradykinin, histamine and prostaglandins. Pain receptors donot adapt to a continuing stimulus. Cytokines, Nerve Growth Factor and other growth factors have been shown as mediators of pain and hyperalgesia associated with tissue injury [6].There is normally a decrease in pain threshold and increase in responsivity with time, so that receptor becomes more sensitive to the pain (hyperalgesia) [7]. Hence, the diseases characterized by chronic pain, namely, migraine, rheumatoid arthritis, osteoarthritis, gout, lumbar and cervical spondylitis, etc. call for a drug delivery system that allows for extended release of

the drug, devoid of the adverse effects associated with the therapeutic regimen. Non-steroidal anti-inflammatory drugs, used to treat such patients are known to cause severe gastrointestinal toxicity, besides other side effects, upon prolonged oral use. Amongst the several causes of pain, the cancer is the most important cause of chronic pain. Cancer itself causes pain through extension into soft tissues [7]. Opioid analgesics are the agents of choice to treat the severe pain associated with cancer. Since, the drug has to be administered frequently for a long period, the drug delivery system should be such that gives the maximum bioavailability of the drug, so that the patient gets the highest therapeutic benefit without getting exposed to high doses [8].

A number of agents are used in the management of pain, such as non-steroidal anti-inflammatory drugs, opioid analgesics, counterirritants and local anaesthetics. Although, oral route of drug administration is the most common, but for the purpose of pain management, topical route is preferred. Advantages of topical route over oral or injectable includes, avoidance of first pass metabolism, ease of application, less fluctuation in drug levels, achievement of efficacy with a lower total dose, simple discontinuation of medication,

site-specific drug delivery, improved adherence and avoidance of risks of drug interaction [9]. In the topical drug delivery systems, the transdermal route of drug delivery is of paramount interest. The present review has been prepared to give an insight into the physical techniques for enhancing drug delivery, focusing on the techniques adopted to improve management of pain and, the research carried out in the recent decades.

Transdermal drug delivery:
Transdermal drug delivery systems (TDDS) encompass the formulations which deliver the medication across the patient's skin[10]. The delivery of drugs across the skin by depends on the physicochemical properties of the drugs, i.e. molecular weight (<500 Da), partition coefficient (1-3) and potency of drug (below 200mg IV dose/ day) [11].

Transdermal delivery represents an suitable means for certain drugs and is an alternative to hypodermic injection too. Transdermal delivery has a number of advantages compared with the oral route. In particular, it is used when there is significant first pass effect of liver, which metabolizes the drugs [3]. Transdermal drug delivery system also has merits over hypodermic injection which is painful, generates dangerous medical waste and carries the risk of disease transmission by needle reuse [12-13].

In addition, transdermal systems are non-invasive and can be self-administered. Moreover, they are capable of providing release for long periods of time (up to one week), improve patient compliance and are inexpensive [12]. Transdermal delivery not only provides controlled, constant administration of the drugs, but also allows continuous input of drugs with short biological half-lives. In addition to these benefits, it eliminates pulsed entry into the systemic circulation.[14]

Owing to these advantages, many transdermal formulations are available in the market for the management of pain e.g. fentanyl iontophoretic transdermal system (ITS), which has found wide clinical use. In order to enhance permeation through the skin, transdermal formulations need permeation enhancement methods. Enhanced

percutaneous delivery of drugs may be achieved by physical or chemical means. In this review, we have attempted to give an overview of the physical methods available for enhancement of transdermal delivery of drug molecules, with special focus on their applications in pain management.

Physical methods for transdermal drug delivery:
Technological advancements in the recent decades helped to overcome the challenges facing transdermal drug delivery. The physical methods which enable the delivery of macromolecules across the skin, primarily involve the application of mechanical, electrical, thermal or magnetic energy. These techniques cause the disruption of skin membrane to permit drug transport. Some of the commonly employed techniques include iontophoresis, electroporation, sonophoresis, use of laser radiation and radiofrequency, microneedles, thermal ablation and so on. The following discussion throws light on the principle of each physical technique and gives an account of the research that has taken place in this arena for the development of transdermal therapeutic systems, focusing on pain management.

Iontophoresis:
Iontophoresis is defined as the application of an electric potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties. This technique is capable of expanding the range of compounds that can be delivered transdermally. The iontophoretic technique is based on the general principle that like charges repel each other. Thus,, during iontophoresis, if delivery of a potentially charged drug is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity. On the application of electromotive force, the drug is repelled and moves across the stratum corneum towards cathode, which is placed elsewhere on the body. Advantages of iontophoresis are-

- Hepatic first pass effect is bypassed and higher patient compliance

- Delivery of ionized and unionized drugs

- Continuous or pulsatile drug delivery and permitting easier transmission of drug delivery.
- Improving delivery of polar molecules as well as high molecular weight compounds
- Systemic delivery or local delivery of drugs[15]

Transdermal drug delivery occurs by a combination of:

- Concentration gradient (diffusive/ passive transport component) and electrochemical potential gradient developed across the skin

- Increased skin permeability under applied electric current i.e. electromigration or electrorepulsion

- A current induced water transport effect (electroosmosis/ convective transport/ iontohydrokinesis) [16]

In iontophoresis charged molecules move via electrophoresis, and the weakly charged and uncharged molecules can be moved by electroosmotic flow of water, generated by preferential movement of mobile cations (e.g. Na^+) in the stratum corneum [12]. Iontophoresis provides usual benefits of transdermal delivery, but it can also be used for programmed and controlled delivery of drugs by adjusting the current [17].

Iontophoresis technique has been extensively applied on analgesics for pain management. A study of the literature revealed that several *in vitro* and *in vivo* studies have been performed with analgesics. Current densities upto 5mA have been used. Iontophoresis enhances the movement of molecules through skin and, hence, it is very successful in pain management.

Of all the available techniques drug delivery enhancement by transdermal route, iontophoresis has been the most widely exploited, majority of research having been carried out with fentanyl. In addition to fentanyl, it has also applied to enhance the delivery of drugs like ibuprofen, indomethacin, etc.

Fentanyl is one of the best agents employed in the severe cases of pain such as cancer pain, postoperative pain management, etc. A lot of work has been performed for the development of fentanyl iontophoretic systems *in vitro* and *in vivo.* Current densities upto 0.5mA have been used in research. Fentanyl iontophoretic transdermal system (ITS) are available in the market, which may be applied to patient's chest or upper arm. Patient self-activates the system by pressing the recessed dosing button twice within 3 seconds. Activation results in low dosing electric current (170μA) flowing through the system. It delivers pre-programmed 40μg of dose for a period of 10 min. Patient can self-administer a maximum of 6 doses per hour. It works for up to 24 hrs or 80 doses, whichever comes first. Fentanyl delivery through iontophoretic systems is very effective and safe. Power I has reviewed the work on fentanyl iontophoretic system. He reviewed the results of US clinical trials from which it was concluded that fentanyl iontophoretic system prove to be an equivalent method for pain control to standard regimen of morphine [19].

Grond S et al, compared fentanyl iontophoretic system with patient controlled analgesia with intravenous morphine and observed that a higher percentage of patients in the fentanyl ITS group reported patient global assessment ratings of 'excellent' at 24 h compared with patients in the morphine [20].

Herndon, compared fentanyl iontophoretic system with intravenous administered fentanyl and observed that in fentanyl iontophoretic system absorption increases in a time dependent fashion over first 10 hrs of dosing. After 24 hrs the other pharmacokinetic parameters were also compared and it was observed that fentanyl iontophoretic system proved equivalent to patient controlled analgesia using i.v. morphine [21].

Jadoul *et al.,* worked on quantification and localization of fentanyl and thyrotropin releasing harmone (TRH) delivery by iontophoresis in the skin. For this purpose, autoradiography and techniques of stripping/slicing were employed, They performed iontophoresis at 0.33 mA/c.m.^{2} for 1, 4, 6 hrs and observed the occurrence of

transepidermal penetration and concluded that transappendageal route is significant with regard to drug penetration [24].

Thysman *et al.,* investigated the effect of electrical and physiochemical factors on the transdermal iontophoresis of fentanyl through hairless rat skin. An increase in current density resulted in higher transderrmal flux while continuous current was found to be more effective in inducing transdermal drug permeation as compared to pulsed current.. A reduction in duration of iontophoretic treatment caused a decrease in the cumulative amount of drug detected in the donor compartment. Further, iontophoresis gave better results at acidic pH. An increase in the drug in the donor compartment yielded greater flux values. The group concluded that electro-osmosis was not involved in the differences observed in the permeation kinetics [25].

Oral doses of ibuprofen result in gastrointestinal toxicity. Hence, it can be suitably used through transdermal route. Ghosh et al prepared ibuprofen prodrugs and carried *in vitro* studies on three different current densities i.e. 0.5, 2.5 and 5 mA/c.m.[2]. For passive permeability, the results showed that prodrug formation was useful only upto addition of one alkyl group (2,4, isobutyl phenyl ethyl propionate) and, thereafter, permeation in rate decreased. Enhanced permeability observed in iontophoresis was significant only at higher current densities (2.5 and 5 mA/cm^{2}) [26].

Sainti *et al.,* studied post-iontophoresis transport of ibuprofen lysine across rabbit ear skin. They used current densities of 0.125, 0.25, and 0.5 mA/c.m.[2] for 60 min and observed that the iontophoresis enhanced the drug permeation [27]. Wang *et al.,* performed iontophoresis and electroporation studies with indomethacin *in vitro* and *in vivo*. Excised wister rat skin, pig skin human epidermal membrane and cellulose membrane were used for *in vitro* studies whereas *in vivo* studies were performed in wister rats. *In vitro* studies were performed using current density 0.5mA/c.m.[2]. It was observed that iontophoresis increased the permeation of indomethacin both *in vitro* and *in vivo*. A synergistic effect was observed when the two techniques were used in combination, along

with a reduction in interspecies differences [29]. Tashario et al investigated the effect of lipophillicity on iontophoresis of non-steroidal anti-inflammatory agents. The drugs selected according to lipophillicity (salicylic acid < ketoprofen < naproxen < indomethacin) were tested in rats (*in vivo*). They used current density at 0.625 mA/c.m.[2] for 90 min and drug concertation was observed in skin, cutaneous vein and systemic vein. It was observed that skin concentration of the drug increased with increase in lipophillicity, whereas cutaneous plasma concentration decreased with increase in lipophillicity. Moreover, transfer of drug from skin to cutaneous vein decreased as lipophillicity increased [30].

Tomoda *et al.,* worked on transdermal delivery of indomethacin and coumarin-6 loaded poly lactose glycolic acid (PLGA) nanoparticles by iontophoresis *in vivo* and *in vitro*. Indomethacin was taken as the model drug, while coumarin-6 was chosen as fluorescent marker. In the *in vivo* studies, they, obtained higher permeation of PLGA loaded nanoparticles of indomethacin, through passive diffusion and iontophoresis (0.05mA/cm^{2}) when compared with indomethacin as free molecules. The *in vitro* studies showed that passive diffusion of PLGA nanpaprticles of indomethacin was greater than that of indomethacin as free molecules. Besides, when iontophoresis (3V/cm) was applied to nanoparticles, the permeation was observed to be higher than that achieved with simple diffusion.[31, 32].

Panus *et al.,* studied the iontophoretic delivery of ketoprofen through human cadaver skin (*in vitro*) and in humans (*in vivo*). The *in vitro* studies were performed at current density 0.5mA/cm^{2} for 3 hours and an increased intracutaneous permeation of ketoprofen was observed as opposed to its passive diffusion.

There was no effect of R- and S- ketoprofen enantiomers on the permeation. The *in vivo* studies were performed at 0.28mA/cm^{2} for 40 minutes. Ketoprofen was detected at 40 minutes time interval (0.88 ± 0.42 *µ*g/ml) from the forearm veins of the ipsilateral arm. Urinary excretion of ketoprofen cumulated to 790 ± 170 *µ*g at 16 h after iontophoresis [39].

Fang *et al.,* performed *in vitro* and *in vivo* studies on iontophoretic systems of diclofenac sodium using different polymer formulations. The investigations were carried out using excised rat skin, human skin as well as cellulose membrane to check the *in vitro* drug permeation. *In vivo* drug concentrations were monitored with the help of microdialysis technique. Current density of $0.5mA/cm^2$ for 6 hours was employed. The polymer solutions based on polyvinylpyrrolidone and hydroxypropyl methylcellulose binary system exhibited greater drug permeability than that obtained through single polymer. Additionally, the effect of formulations on drug permeation through cellulose membrane was found to vary from those through the rat and human skin, owing to difference in permeation pathways [40].

Gao *et al.,* performed iontophoretic studies on transdermal delivery of diclofenac sodium gel. Diclofenac sodium gel was prepared using polyvinyl alcohol, carboxymethylcellulose sodium and hydroxypropyl methylcellulose. The diclofenac blood levels were checked in rabbits. The rabbits were divided into four groups, namely: passive diffusion, laurocopram pretreatment, iontophoresis (current density controlled at 0.3 $mA/cm^{2)}$ and combined laurocapram pretreatment and iontophoresis.

The results signified the combination of laurocapram pretreatment and iontophoresis induced enhancement of transdermal delivery of the drug, devoid of any significant skin damage.[41]

Riecke *et al.,* compared the plasma and tissue levels of diclofenac through iontophoretic delivery and passive diffusion, where the gel formulation was topically applied to human volunteers, in a cross-over design. The drug concentrations were analysed in plasma and microdialysis perfusates from the underlying tissue. The researchers inferred that iontophoresis of diclofenac was not superior to traditional topical application, since no differences were observed between the tissue concentrations achieved through the two methods. Also, a higher frequency of skin reactions was observed with iontophoresis [42].

Brickman *et al.,* carried out a study on 39 human participants, 21 serving as treatment group and 18 as control group. This group of researchers conducted a comparative study to evaluate pain relief provided by lidocaine-HCl and dexamethasone delivered via iontophoresis versus oral NSAID therapy alone, for treating acute soft tissue injuries. The reduction in pain levels were recorded on visual analog scale. The results obtained suggest that the reduction in pain levels for the treatment group were much greater as compared to the control group. Also, the number of oral NSAIDs required for effective pain management was effectively reduced [43].

Gratieri *et al.,* studied the iontophoretic delivery kinetics for ketorolac. In the first part of the investigation, then effect of experimental conditiond on the ketorolac delivery via iontophoresis was evaluated using porcine and human skin. Later experiments conducted on male wistar rats were carried out investigate the enhanced delivery of ketorolac to muscular tissue by iontophoresis. The results indicated a promising potential for the use of this system for clinical management localized inflammation and pain [44].

Tavakoli *et al.,* developed celecoxib gels with various polymers, viz. sodium alginate, sodium carboxy methyl cellulose, HPMC K4M and Carbopol 934P. The gels were evaluated for their physicochemical properties. The gels were later tested for the cumulative drug release via passive diffusion and iontophoretic drug delivery using current density $0.3mA/cm^2$ and $0.5mA/cm^{2,}$ respectively. The results demonstrated that the iontophoresis assisted drug delivery resulted in much greater flux values, in comparison with passive diffusion [45]. Guang Yan devised an anode iontophoretic system for the topical delivery of cationic prodrugs to local tissues. The system could be utilized for the local delivery of NSAIDS and anesthetics [46].

The details of studies conducted on iontophoretic systems for transdermal delivery in pain management are given in **Table 2**.

TABLE 2: DETAILS OF IONTOPHORETIC SYSTEMS FOR PAIN MANAGEMENT

Drug	Experimental conditions	Iontophoresis conditions	Conclusion	References
Aspirin	New Zealand white rabbit	$5mA/cm^2$, 10 min	Safe administration of aspirin by controlled iontophoresis	18
Flubiprofen	Male wister rat	$0.4mA/cm^2$, 15 min	Increased dermal delivery	28
Meloxicam	Male wister rat dorsal skin, human skin	$0.5mA/cm^2$, 3 hrs	Enhanced permeation of meloxicam *in vitro*	33
Pentazocine	Cellophane membrane	10,25 and 40 V, duty cycles (50%-55%), 60 min, 1 MHz	40V, 55% duty cycle, maximum transport of drug	34
Lidocaine (cream 4%)	Human (*in vivo*)	2 mA, 10 min	Quick action of lidocaine and good analgesia is produced	35
Lignocaine EMLA cream (5%)		$0.1-0.2 \ mA/cm^2$, 10 min		36
Tramadol	Human	4 mA, 20 min.	Beneficial for relieving pain of knee osteoarthritis	37
Ketorolac	Rat skin (*in vitro*)	$0-0.50 \ mA/cm^2$ and $0.5 \ mA/cm^2$	Transdermal penetration of drug enhanced	38
Salicylic acid	Male spraguedawley rats (*in vivo*)	Current density $0.625mA/cm^2$, duration 90 min	Increased absorption of salicylic acid	30
Naproxen	Male spraguedawley rats (*in vivo*)	$0.625mA/cm^2$, 90 min	Enhanced permeation of naproxen	30
Naproxen (gel)	Human	$0.08- 0.004mA/cm^2$	Pain from lateral epicondylitis is reduced	47
Piroxicam (0.5% gel, Geldene)	Human volunteers (forearm)	$0.3 \ mA/cm^2$, 30, 60 and 125 min	Enhanced drug uptake into the stratum corneum	48
Piroxicam (gel)	Mouse skin (*in vitro*)	$0.07-0.5 \ mA/cm^2$, 6 hrs	100-1000 times more diffusion by iontophoresis than passive diffusion	22
Methadone	Human forearm (*in vivo*)	Weak direct current of 50µA, 4 min	Beneficial for treating painful skin disorder locally	49
Magnesium sulfate	Human volunteers	$1.0 \ mA/cm^2$, 10 min	Analgesic effect produced with good pain relief	50
Hydramorphone	Pig and human skin	1.2 mA, 12 hrs 125 $\mu A/cm^2$ (pig skin)	Concentration independent *in vitro* release	51
Nalbuphine	Wister rat, mice, human skin	$0.3mA/cm^2$	Increased delivery of drug and its prodrugs	52

Laser radiations and Photochemical Waves:
Laser radiations are well used in clinical practices. Direct and controlled exposure of skin to laser radiations results in ablation of stratum corneum, without significant damage to underlying epidermis. Stratum corneum removal enhances the delivery of lipophilic and hydrophilic drugs. Pressure waves generated by laser radiations increase the permeability of the skin [53].

Laser radiations can also enhance the permeation of analgesics through skin. The *in vitro* delivery of diclofenac sodium through the intact and laser porated porcine and human skin was studied by Bachhav *et al*. They performed the investigations using the aqueous formulation, formulation containing propylene glycol and marketed formulation. Cumulative drug permeated and skin deposition were determined. The results obtained from the experiments signified that laser microporation increased the diclofenac transport, from both simple and semisolid formulation [54]. Laser based systems have also been developed for the delivery of indomethacin, nalbuphine and lidocaine by various groups of researchers [55].

Electroporation:
Transdermal electroporation is the application of short (<1s), high voltage (50- 500 V) pulses to the skin to cause disorganization of the stratum corneum lipid structure, resulting in enhanced drug delivery [15]. Electroporation refers to an increase in the permeability of cell membrane caused by an externally applied electric field and has been studied in lipid bilayers [56]. The degree of permeabilization can be controlled by the pulse

duration and pulse number i.e. longer the pulse, greater the perturbation of the membrane in given area [57].

Voltage, number of pulses, pulse length and physiochemical properties of drugs are among the factors affecting drug permeation in electroporation. Two types of electrical pulsing protocols have been used, exponentially decaying pulses (ED) and square wave pulses (SW) [15].

Flux enhancing mechanisms of electroporation are electropermeabilization, electrophoresis and electroosmosis (electric field induced convection). Electropermeabilization is the spontaneous formation of metastable pores due to energy of electric field. Minimum voltage or electric field required to induce pore formation is around 0.2- 1.0 V per lipid bilayer. During electroporation, new electric current pathways are created in the stratum corneum which can be reversible or irreversible type [58]. The table 3 given below provides detailed description of electroporation systems developed for pain management.

TABLE 3: ELECTROPORATION SYSTEMS FOR PAIN MANAGEMENT

Drug	Experimental condition	Electroporation conditions	Conclusion	References
Indomethacin	Male wister rat skin, pig skin, human skin and cellulose membrane	300V,10 min, pulse duration is 200ms, 1 pulse per 30 sec	Enhanced *in vitro* and in vivo skin permeation	29
Meloxicam	Wister rat skin, human epidermal membrane	300V, 10 min, pulse duration is 200ms, 1 pulse per 30 sec	Enhanced *in vitro* and *in vivo* skin permeation	33
Fentanyl	Rats	100 V-500 ms (15 pulses), 250V-200ms(15 pulses), 500V-1.3 ms(60 pulses) 600 ms pulses with pulse spacing 1 min	Rapid increase in fentanyl plasma levels	23
Fentanyl	Hairless rat skin		Significant transport of fentanyl occur	59
Naltrexone	Human skin (*in vitro*)	1 KHz with maximum voltage 300mV	Enhanced skin permeation	60
Proopiomelanocortin	Sprague dawley rats	Two pulses of a 200V current (75ms per pulse with a minimum 2 min interval)	Successfull intrathecal delivered	61
Nalbuphine	Mouse skin, wister rat skin (*in vitro*)	300V, 200ms. 1 pulse per 30 sec applied for 10 min	Enhanced permeation of drug	62

Ultrasound:
Ultrasound is the migration of drug molecules through the living, intact skin and into the soft tissue under the influence of ultrasonic radiations [63]. Ultrasonic radiations in the frequency range 20 KHz to 20 MHz can be used [64]. Ultrasound is a localized, non-invasive, convenient and rapid method of delivering low molecular weight as well as high molecular weight drug molecules into the skin [65]. The **Table 4** describes overview of the type of ultrasound radiations.

TABLE 4: CLASSIFICATION OF ULTRASOUND RADIATIONS [65]

Ultrasound condition	Frequency range	Application
High frequency or diagnostic ultrasound	3-10 MHz	Clinical imaging
Medium frequency or therapeutic ultrasound	0.7-3.0MHz	Physical therapy
Low frequency or power ultrasound	18-100 KHz	Lithotripsy, contract emulsification, liposuction, cancer therapy, dental descaling and ultrasonic scalples[3]

The mechanisms involved in the enhancement of transdermal delivery using ultrasound are lipid alteration of stratum corneum, convection and pore induction (cavitation) [58]. Ultrasound is well tolerated and chances of hepatic and renal injury are very less. Because of these reasons it is much more advantageous [73]. Majority of research work reported for this technique to deliver NSAIDs has been conducted on diclofenac and ibuprofen. The reported studies have been summarized below:

Diclofenac is the most widely prescribed drug for pain management, which also employed for topical application to relieve pain. The transdermal delivery of diclofenac is significantly enhanced by ultrasound treatment and this technique is frequently used in sports related injuries. Hsieh, investigated the effects of ultrasound and diclofenac phonophoresis on inflammatory pain relief by measuring the nitric oxidase synthase expression. He induced inflammatory arthritis in 18 male wister rats using intra-articular tibiotarsal injection of complete Frenud adjuvant (CFA). They divided the infected animals into three categories i.e. ultrasound, diclofenac phonophoresis and sham treatment. At the end of the test it was inferred that ultrasound and phonophoresis treatments probably modulate the CFA induced increase in nitric oxidase. It was also concluded that peripheral use of diclofenac phonophoresis provides little benefit over ultrasound in affecting central mechanism of nociception [66, 67].

Similarly, Sharma *et al.,* compared pain relief provided by diclofenac and ketoprofen phonophoresis treatment. The study was carried out on 150 Lybian patients. All the patients were treated using ultrasound at a frequency of 1 MHz with intensity of 1 W/cm^2, three times a week for two continuous weeks. The pain levels were measured with the aid of visual analog pain scale. The results at the end of two weeks indicated that the pain levels were reduced with both treatments, however, the treatment with ketoprofen gel was more effective. They concluded that the process of therapeutic phonophoresis with ketoprofen gel is significantly moreeffective than diclofenac gel in reducing pain of soft-tissu einjuries of knee joint. Heim, used ultrasound at 0.8-1.2 MHz for 5 min

and found that ultrasound is valuable addition to existing treatment modalities for minor sports related injuries when studied in humans [69]. Rosim *et al.,* worked on Volteran emulgel (Novartis) at frequency 1MHz and intensity 0.5 $Watt/cm^2$ in humans and reported that previously applied therapeutic ultrasound irradiation enhances the percutaneous penetration of the topical diclofenac gel [70].

Baky *et al.,* compared the efficacy of ibuprofen phonophoresis with topical application of ibuprofen in improvement of hand grip strength in psoriatic arthritic patient. The study was conducted on 40 patients, divided into two groups. The first group received routine physical therapy along with sham ibuprofen phonophoresis. On the other hand, the second group was treated with routine physical therapy and ibuprofen phonophoresis. The patients were evaluated for grip strength, tender and swollen joint count, both before and after receiving the treatment. The ultrasound conditions were frequency 1MHz and intensity 1.5 W/cm^2. They reported enhanced delivery of ibuprofen facilitated by phonophoresis, resulting in greater grip strength[73].

Kozanoglu *et al.,*compared the effectiveness of ibuprofen phonophoresis with conventional ultrasound. 60 patients were randomly assigned to phonophoresis or conventional ultrasound condition of frequency 1MHz and intensity 1.5 $W/cm^2$for 5 min to target knee joint. They concluded that both therapeutic modalities were found to be effective and generally well tolerated after 10 therapy sessions. Ibuprofen phonophoresis was not superior to conventional ultrasound treatment in patients with knee osteoarthritis [74].

Meshali *et al.,* studied the effect of formulation composition and ultrasound on permeation of ibuprofen across polymeric and biological barriers. They used rabbit skin and cellulose membrane for *in vitro* testing while *in vivo* studies were conducted as rabbit as the animal model. An ultrasound intensity of 1.5 W/cm^2 was employed. They observed that transport of ibuprofen through skin depended on formulation variables. Higher transport was obtained with cellulose membrane. Moreover, gel formulation yielded greater transport

of the drug as compared to oleaginous or emulsion based preparations, which also depends on thickness of the gel and concentration of formulation additives. Transport increased with increase in alcohol concentration and decreased with increasing propylene glycol concentration. They reported 11-fold increase in drug permeation by ultrasound and concluded that the aqueous gel formulations act as ideal coupling agent for cutaneous delivery of drugs [75].

Brucks *et al.,* developed an *in vitro* method to investigate the effect of ultrasound on the *in vitro* absorption of ibuprofen from a propylene glycol/water vehicle through human epidermis. They concluded that ultrasound yields increased penetration of ibuprofen through human skin. They also observed that evaporation of vehicle components may alter the skin/vehicle partition

coefficient, decreasing the effects of ultrasound on the penetration of ibuprofen through the skin[76]. Serikov compared the efficacy of ibuprofen (nurofen gel) upon conventional topical application and ultraphonophoresis of the same in osteoarthrosis patients.

He applied ultraphonophoresis of 5% nurofen gel to 20 patients with afflicted joints. The pain relief was measured with the help of visual analogue scale. The findings of the study indicate an initial intensification of the pain followed by significant pain alleviation[77]. Most of the applications of ultrasound in pain management can be attributed research carried out on diclofenac and ibuprofen, nevertheless other drugs like ketoprofen, ketorolac etc. have also been used with ultrasound technology. The studies performed with other drugs have been outlined in **Table 5**.

TABLE 5: TABLE SHOWING DETAILED DESCRIPTION OF ULTRASOUND SYSTEMS FOR PAIN MANAGEMENT

Drug	Experimental conditions	Ultrasound conditions	Experimental conclusion	References
Fentanyl	Human and rat skin	20KHz, 2.5 w/cm^2	Enhanced transport of fentanyl across human and hairless rat skin	71
Flufenamic acid	Skin (*in vitro*)	1.5 W/cm^2, 5-30 min	Highest penetration at 1.0 W/ cm^2 after 30 min	72
Indomethacin	rats	1 MHz, 0.25, 0.5, 0.75 & 1 W/ cm^2	0.75W/cm^2 for 10 min was found to be most effective	78
Ketoprofen	Human	1MHz, 1 W/cm^2	Enhanced Ketoprofen delivery	68
Ketoprofen		50% Duty cycle		
Ketoprofen gel	Human	1MHz ,1.5W/cm^2	High local concentration with enhanced delivery	67,79
	Human (*in vivo*)	0.8 W/ cm^2	Support the application of phonophoresis with ketoprofen	80
Ketorolac	Rat skin (*in vitro*)	1 MHz, 1-3 W/ cm^2, 30 min	Significant increase in ketorolac permeation at 3 W/ cm^2	81
Ketorolac	Rat		Useful for treating inflammation and pain transdermally	82
Lignocaine	Human	870 KHz, 2.0 W/ cm^2	Marginal increase in rate of absorption	83
Lidocaine		0.5 & 1 MHz, 2.0W/ cm^2	0.5 MHz ultrasound is more effective than 1.0 MHz	
	Human			84
Lidocaine	(*in vivo*) mice	48 KHz, 0.17 W/cm^2	Rapid analgesic effect	85
Morphine	Hairless mouse skin	40 KHz, 0.5 W/ cm^2	Increased permeation of drug	86
Naproxen	Human	1 MHz, 1W/cm^2	Effective electrotherapy method	47
Piroxicam	Male wister rat	870 KHz, 1 W/ cm^2	10 times increase in piroxicam diffusion through the skin	87

Magnetophoresis:
Magnetohoresis involves the application of magnetic field which acts as an external driving force to enhance the diffusion of diamagnetic drug molecules through the skin [53, 88]. Magnetic field

results in rupture of the skin and ultimately increases skin permeability. Magnetism or magnetic chip technology ensures pulsatile and controlled drug delivery [88]. Use of magnetophoresis for pain relief has not been reported till date.

Microneedle:

Microneedles are the micron scale devices that are employed for transdermal drug delivery [89]. Solid needle arrays create pores in the skin by penetrating the stratum corneum. This enhances the transdermal transport of drug- coated needle arrays which transfer the drug into the skin. Upon application to the skin, drug-coated needles penetrate it and deliver the drug from the drug coated surface into the epidermal layer [58].

Microneedle concept was proposed in 1970 but was demonstrated in laboratory after 1990's. After the initial studies in 1998, this field has attracted the interest of many scientists. The micro scale holes created by microneedles have been found to be safe and also smaller, than holes caused by hypodermic needles [90].

In recent study, on a 0-100 pain scale, in human subjects, microneedleinsertion score 6 ± 5 as compared to 24 ± 16 for injections by hypodermic needles, was recorded. This study was performed on naltrexone having 5*10 arrays of 620μm long stainless steel needles [91].

Microneedles for drug delivery are made up of wide variety of designs and materials. These can be solid, hollow, fabricated from silicon material and plastic materials such as polycarbonates. Microneedles have hundreds of needles per array, ranging in size from 100 microns to 2 mm [8, 92].

System designed by combining microneedles with a patch like structure has all favorable properties i.e. ease of use, continuous release and painlessness [93]. In the context of pain management systems, Zhang *et al.,* has prepared lidocaine hydrochloride coated microneedles and this system was found to enhance the efficacy of lidocaine hydrochloride [94]. Brogden *et al.,* undertook a study to demonstrate the delivery of naltrexone for seven days post microneedle application in human subjects. Diclofenac was chosen as the placebo drug and impedance measurements were done to check microporeformation.

Further, the plasma concentrations of naltrexone were analysed [95]. McCrudden *et al.,* formulated and evaluated polymeric microneedle arrays for the delivery of high dose, low molecular weight drugs. Ibuprofen sodium was taken as the model drug whereas poly(methylvinylether/maleic acid) was chosen as the copolymer. Approximately 90% of the loaded drug was delivered over a period of 24 hours. Biocompatibility studies and *in vivo* rat experiments confirmed the safety of the developed system [96]. Ghosh *et al.,* developed a codrug approach to achieve drug delivery across microneedle treated skin. The study was carried out with naltrexone and diclofenac. *In vitro* and *in vivo* experiments were taken up to check for atability, bioconversion and permeation [97].

Microdermabrasion:

Microdermabrasion involves the removal of stratum corneum barrier by simply using sandpaper. This method has cosmetic applications too[12].

The rupture of outer layer of the skin facilitates the permeation of topically applied medications [53]. In the management of pain, this method has shown to enhance the penetration of the lidocaine [12].

Needleless injections:

Needleless injections are the devices which do not require hypodermic needles for drug administration [98, 53]. The drug molecules are passed through the skin with high speed by a suitable energy source, which enables transdermal delivery of molecules [53]. Pressure produced by using either a gas (CO_2, He, N) or a spring device provides the energy required for drug delivery. Pressure induced permeation allows the medication to pass through the skin [98].

Needle less injections have been explored for the delivery of lidocaine hydrochloride, with the view to provide pain relief [53]. Jo Woodward developed a single-use, needle less drug delivery device for the administration of opoids to patients who suffer from chronic pain, such as those suffering from cancer [99].

Radiofrequency:

Radiofrequency encompasses the application of high frequency alternating current (~100 KHz), which permits the formation of heat induced microchannels in the cell membrane. The number and depth of microchannels determines the rate of

drug delivery. The number and depth of microchannels depends upon the microelectrodes being used [53, 100]. Radiofrequency has not found applications in pain control systems yet.

Thermal ablation:
Thermal ablation is a non-invasive technique to remove small portions of the stratum corneum, in order to increase the skin permeability, via micro-scale channels into the skin. Transdermal drug delivery by this technique is accomplished by heating the skin surface, with the view to vaporize tissues. This results in the removal of stratum corneum at the site of heating [101]. As a result of heating, kinetic energy of the proteins, lipids, carbohydrates and drug molecules present in the cell membrane, increases [100]. Recently published studies have suggested that temperature should be above the boiling point of water, which leads to tissue combustion [12]. The use of thermal ablation in pain management has not been reported so far.

CONCLUSION: The potential advantages of transdermal route of drug administration over the oral and parentral route propelled the research efforts in this field. The non-invasive methods of drug delivery by this route promise safe and effective means of delivering the active agent to the systemic circulation, with the choice of administering the drugs through multiple sites. But the excellent barrier properties of the skin pose a challenge for the delivery of many drug molecules, especially macromolecules and hydrophilic drugs. However, with the emergence of technological breakthrouhgs, the challenge could be overcome to a great extent.

Techniques such as iontophoresis, electroporation, sonophoresis and microneedle array systems have proved highly beneficial in this aspect. Each of the available technique has its own unique advantages as well as limitations. And the inherent features of each technique also offer the possibility of using them in combination, which could further enhance drug bioavailability and shorten treatment time.

The merits of the physical techniques for percutaneous drug delivery have been well utilized for the design and development of therapeutic systems intended for pain relief. Pain, being the main symptom of many ailments and injuries, can vary in nature and intensity. Effective pain management, therefore, calls for drug delivery systems which allow flexibility in dose administration, prolonged pain relief and minimal adverse effects on continuous use. The investigations in this arena have yielded promising results. Evidently, some of the therapeutic systems based on these techniques have also been marketed and are being used in clinical settings.

However, more studies are required to be undertaken to look into the mechanism of drug delivery and dermatokinetics of these delivery systems. The basic research work carried out in the laboratory needs to be taken forward in clinical trials, which would propagate further research in the area. Drug delivery systems involving the lesser utilized techniques such as radiofrequency, thermal ablation and laser technology can be anticipated. The high cost of these techniques is a deterrent in their extensive application. Many investigations are in progress to address this concern and with the advent of portable devices, it is likely that the applications of these techniques will further boost disease management.

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