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# Formulation Development of SNRI-Loaded Transdermal Drug Delivery Systems for Chronic Musculoskeletal Pain: A Critical Review

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**ABSTRACT**

Chronic musculoskeletal pain (CMP) is a major global health concern associated with persistent pain, functional disability, and reduced quality of life. Conventional oral pharmacotherapy, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen, often presents limitations such as gastrointestinal adverse effects, hepatic toxicity, poor patient compliance, and first-pass metabolism. Serotonin–norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine and venlafaxine, have emerged as effective therapeutic agents due to their dual analgesic and antidepressant actions. However, oral SNRI administration is associated with fluctuating plasma concentrations and systemic side effects. Transdermal drug delivery systems (TDDS) provide a promising alternative approach for the sustained and controlled delivery of SNRIs through the skin. TDDS bypass hepatic first-pass metabolism, maintain steady plasma drug concentrations, improve bioavailability, reduce dosing frequency, and enhance patient compliance. This review discusses the formulation development of SNRI-loaded transdermal patches, including polymer selection, penetration enhancers, plasticizers, adhesives, and backing membranes. Various preparation techniques such as solvent casting, solvent evaporation, and micro reservoir methods are highlighted. The review also summarizes evaluation parameters including physicochemical characterization, drug content uniformity, in vitro release, ex vivo permeation studies, adhesion testing, and skin irritation assessment. Furthermore, emerging technologies such as, microneedles, iontophoresis, and smart patch systems are explored for enhancing transdermal SNRI delivery. Overall, SNRI-loaded TDDS represent an innovative and effective strategy for chronic musculoskeletal pain management, offering improved therapeutic efficacy, safety, and patient adherence compared with conventional oral therapy.

**Key words**: Chronic musculoskeletal pain (CMP), Transdermal drug delivery systems (TDDS), Serotonin–norepinephrine reuptake inhibitors (SNRIs),SNRI-loaded transdermal patches.

## 1. INTRODUCTION

### 1.1 Global Burden of Chronic Musculoskeletal Pain

The term "chronic musculoskeletal pain" (CMP) refers to more than 150 conditions that impact the human motor system, including fibromyalgia, myofasciitis, low back pain, limb pain, neck and shoulder pain, and chronic joint pain. Twenty to thirty-three percent of the world's population suffers from musculoskeletal diseases. Although CMP prevalence statistics differ between research, it is evident that the illness increases with age. Low back pain is the most common of these conditions, affecting 30 to 40 percent of individuals. According to a recent US survey, CMP affects 50% of all individuals, which is equivalent to the combined prevalence of chronic respiratory and cardiovascular disorders. [1]

### 1.2 Classification of Chronic Musculoskeletal Pain

CMP encompasses a variety of clinical disorders categorized by anatomical features and cause. [2] Pain is categorized as primary when it cannot be attributed to a recognized illness. Pain is categorized as secondary when it results from an illness that affects the muscles, soft tissues, joints, and bones.[3] Other ailments include fibromyalgia syndrome, osteoarthritis, rheumatoid arthritis, low back pain, neck discomfort, and inflammatory/degenerative diseases.[4] Central nervous system diseases with severe spasticity produce musculoskeletal pain manifestations.[5] The International Association for the Study of Pain (IASP) established comprehensive classification system for chronic pain in ICD-11, providing standardized diagnostic criteria and nomenclature. Despite biological differences, CMP conditions share common clinical phenotype: persistent pain, activity limitation, emotional distress, decreased socialization, employment inability, loss of independence, and heightened future anxiety. [6]

After then, ICD-11 distinguished between primary and secondary pain and incorporated the biological, psychological, and social facets of the complicated experience of chronic musculoskeletal pain. Fibromyalgia, CPRS-1, and non-specific low back pain are examples of the clearly defined category of primary chronic musculoskeletal pain. [7] On the other hand,

prolonged nociceptive stimulation to musculoskeletal structures is the cause of secondary chronic musculoskeletal pain, which is a sign of a different illness. Additionally, it may be brought on by (i) chronic inflammation brought on by active or latent infections, crystal deposition that causes acute inflammation, or autoimmune and autoinflammatory diseases; (ii) structural alterations like osteoarthritis, spondylosis, or musculoskeletal injuries; and (iii) nervous system disorders like Parkinson's disease, multiple sclerosis, and peripheral neurological disorders. [8]

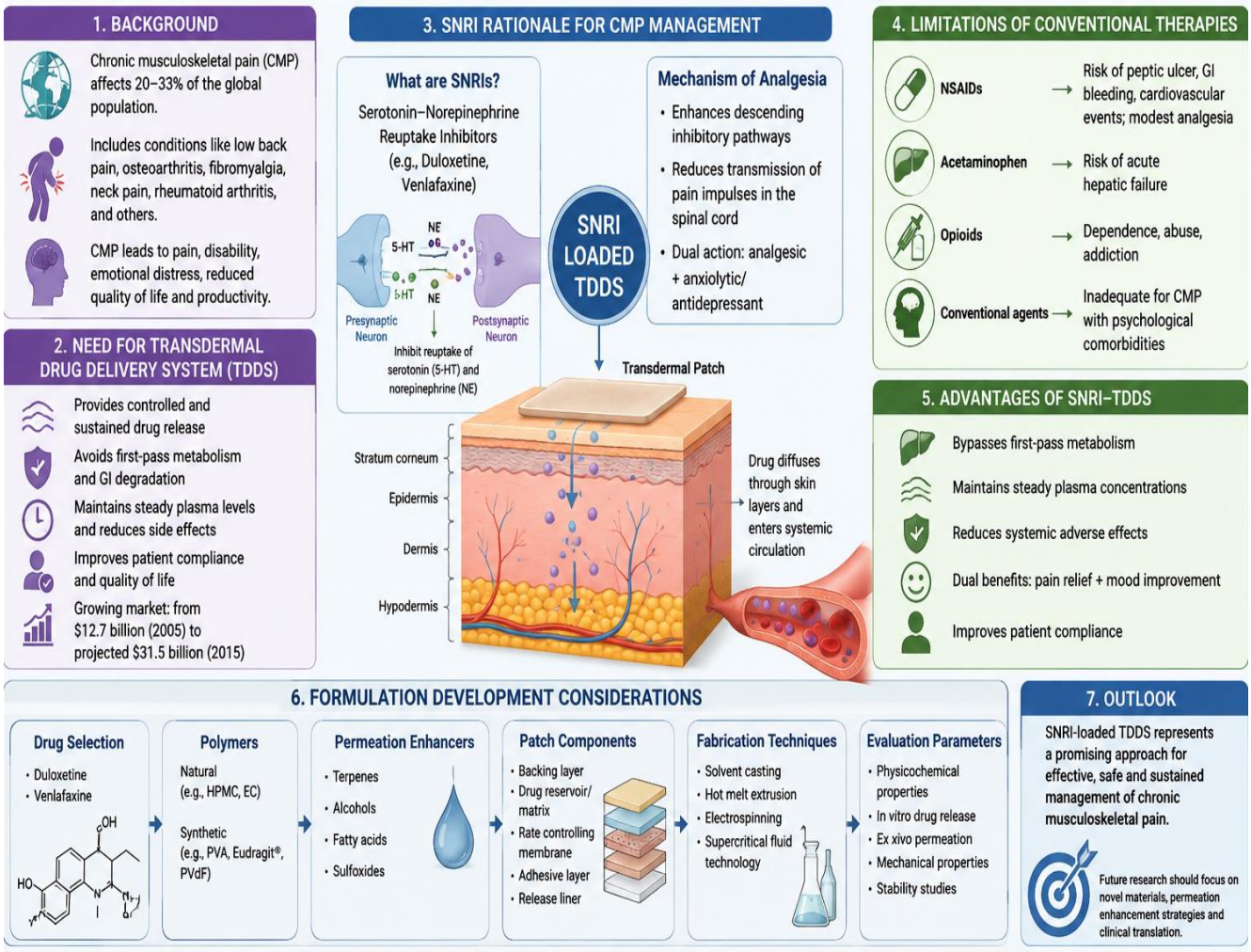



**Fig No:1 GRAPHICAL REPRESENTATION**

## 1.3 Need for Transdermal Drug Delivery System.

In recent years, TDDS has become one of the most inventive subjects for drug delivery. For a wide range of pathophysiological conditions, such as hypertension, angina pectoris, motion sickness, female menopause, and male hypogonadism, more than 35 transdermal drug delivery products have been approved in the United States (Barry 2001). [9] Approximately 40% of drugs are being investigated to confirm their viability for transdermal drug delivery. This fact makes the transdermal delivery system's success in the pharmaceutical industry clear. In 2005, the market share for transdermal delivery was $12.7 billion; it rose to $21.5 billion in 2010 and is projected to reach $31.5 billion in 2015. [10]

Transdermal drug delivery systems (TDDS) are self-contained, discrete dosage forms that deliver the drug(s) to systemic circulation through the skin at a controlled rate when applied to intact skin. The transdermal route of administration is considered as one of possible route for the local and systemic delivery of drugs. [11] Transdermal delivery provides the advantages of controlled and constant drug delivery and continuous delivery of drugs with

short biological half-lives, and eliminates pulsed systemic circulation, which often causes undesirable side effects. Different forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc thus emerged [12]

### 1.4 Introduction of SNRI.

SNRIs are a type of antidepressant medications that are often used in therapeutic settings. They are examplified by duloxetine and venlafaxine. [13] Research has demonstrated that SNRIs significantly reduce several types of chronic musculoskeletal pain by acting as analgesics and antidepressants. Increasing the descending inhibitory system's function and lowering the pain stimulation impulses sent through the spinal cord are the two major ways that SNRIs reduce CMP pain. [14]

### 1.5 Therapeutic Limitations and SNRI Rationale

Existing pharmacotherapeutic options present significant limitations compromising treatment efficacy.[11] NSAIDs increase risk of peptic ulcer, gastrointestinal hemorrhage, and cardiovascular events with modest analgesic efficacy.[15] Acetaminophen carries risk of acute hepatic failure.[13] Opioids cause dependence, abuse, and addiction.[14] Conventional agents inadequate for concurrent CMP and psychological comorbidities.[15] SNRIs provide dual analgesic and anxiolytic-antidepressant effects.[16] Duloxetine, sole FDA-approved antidepressant for CMP, established in 2010 as primary pharmacological option.[17,18] SNRI-based transdermal delivery bypasses first-pass metabolism, maintains steady plasma levels, reduces adverse effects, and improves compliance.

## 2. Transdermal Drug Delivery Systems

### 2.1 Introduction on Transdermal Drug Delivery System

Nowadays, 74% of medications are taken orally and are not as beneficial as most people would want. Transdermal medication delivery systems were developed in order to promote such traits. [20] With the development of modern pharmaceutical dosage forms, the transdermal drug delivery system (TDDS) became acknowledged as a key component of innovative drug delivery systems. [21] Despite being more expensive than traditional formulations, transdermal dosage forms are growing in popularity due to their unique benefits. [22] Improved bioavailability, controlled absorption, more consistent plasma levels, painless and fewer side effects, ease of application, and the flexibility to stop drug administration by simply removing the patch from the skin are some of the potential benefits of transdermal drug delivery.[23]

Transdermal drug delivery systems are novel pharmaceutical formulations that provide drugs systemically via the skin. [24] Compared to traditional methods of administration, transdermal distribution has a number of benefits, including extended-release kinetics, non-invasiveness, and avoidance of first-pass metabolism. [25] For medications that need to be released continuously or under control over an extended length of time, this approach is quite beneficial. [26]

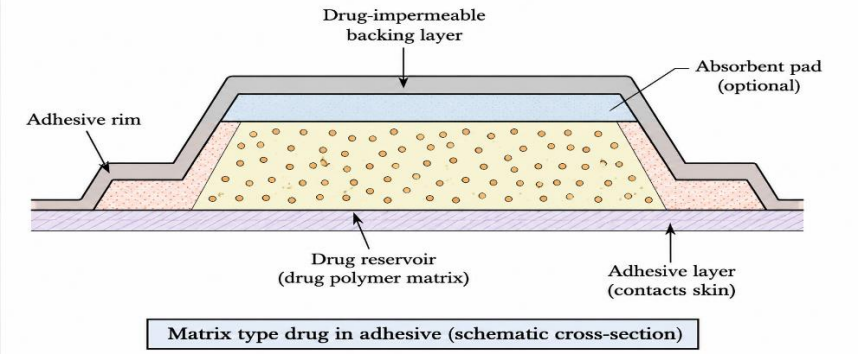
### 2.2 Limitations of TDDS

Transdermal patches cannot deliver ionic drugs. Transdermal patches cannot sustain elevated medication levels in blood or plasma. Transdermal patches are unable to provide pulsatile medication delivery.[27] **Limited Types of Drugs:** Not every medication may be successfully used topically. Transdermal administration is only appropriate for medications with specific physicochemical characteristics, such as tiny, lipophilic, and low molecular weight.[28] **Skin Barrier**: Drug penetration is prevented by the stratum corneum, the skin's outermost layer. The types of medications that may be administered transdermally and the rate at which they can be absorbed are both limited by this barrier. **Rate of Absorption**: Transdermal drug delivery tends to be slower compared to other routes such as oral or intravenous administration. This limits the usefulness of transdermal patches for drugs that require rapid onset of action. [29] **Skin Irritation**: Some drugs or components of the transdermal patch can irritate the skin, leading to local reactions such as redness, itching, or rash. **Size Limitation**: The size of the drug molecule can limit its ability to penetrate the skin. Large molecules may not be able to pass

through the skin barrier effectively. [30]. **Dose Limitation**: Transdermal patches have a limited capacity to deliver high doses of drugs. The size of the patch and the rate of drug release can restrict the amount of drug that can be administered transdermally.[31]

## 2.3 Types of Transdermal Systems.

Transdermal patches were categorized into six main types: which includes Single layer drug in adhesive. Multilayer drug in adhesive.



Matrix type drug in adhesive (schematic cross-section)

**1. Matrix type**: Matrix type of transdermal patch was designed in the year 1990s. Here, the patch is very slim and less visible when sticked on the skin. In this type, the film controls release of medication from the patch. [32] In this method, the drug and polymer dissolved in solvent (soluble) or insoluble drug homogeneously dispersed in hydrophilic or lipophilic polymer. To the above, add required quantity of plasticizer and permeation enhancer. [33] Medicated polymer formed is then molded into the ring with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. [34] Thus, film formed is separated from the ring and mounted onto the occlusive base plate in a compartment fabricated from a drug impermeable backing. [35] Then, an adhesive polymer is then spread along the circumference of the film. A few examples of matrix type transdermal patches are Nitro-glycerin transdermal patch-Nitro Dur®. [36]

### Advantages

Avoidance of first-pass effect. Avoid gastrointestinal track difficulties which are caused by enzymes and food interactions. Stable and controlled blood level. Ease of termination of drug action if necessary. Poor oral bioavailability. Narrow therapeutic window. No interference with gastric and intestinal fluids. Less chances for overdose.

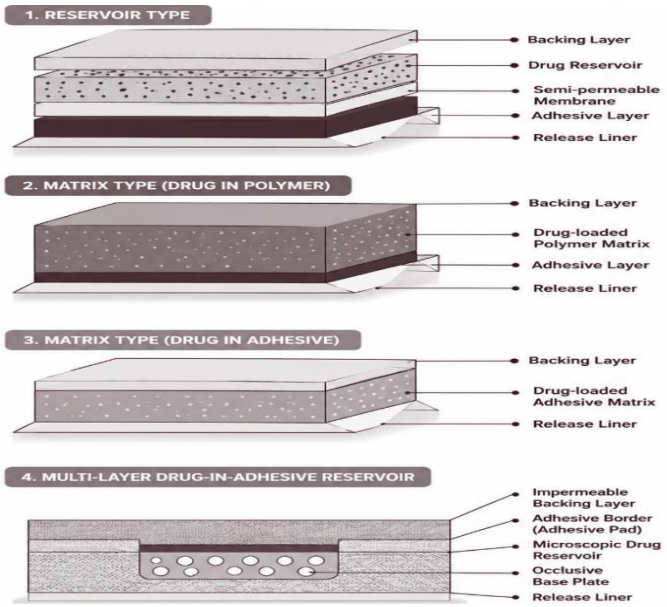
### Disadvantages

The transdermal delivery is unsuitable when the dose is high. Drug is skin sensitizing, skin irritating and it gets metabolized in skin. Drug undergoes protein binding in skin. Drug is highly lipophilic or hydrophilic.

**2. Reservoir type:** It is different from single layer drug in adhesive and multilayer drug in adhesive systems. It is having separate drug layer. In this, the drug reservoir layer is a liquid compartment which is consisting of drug solution or the suspension where the drug particle is suspended in silicon fluid gives paste such as suspension/gel/clear solution in ethanol, which is separated by the adhesive layer. The rate controlling membrane is prepared by solvent evaporation or compression method. This patch is also consisting of backing layer. Advantage of this type is it follows true zero order release to achieve a constant serum drug level, for example: Duragesic, Estraderm, and Androderm. Membrane matrix hybrid It is the modified form of reservoir matrix in which the liquid form of drug reservoir is replaced with solid matrix polymer (polyisobutylene), example for this type is Catapress. [37]

**3. Micro reservoir type:** In this type, the drug is suspended in an aqueous solution of water miscible drug solubilizer poly ethylene glycol (PEG) or drug suspension is homogenously dispersed by a high shear mechanical force in lipophilic polymer, forming 1000s of unleachable microscopic drug particles. The dispersion is quickly stabilized by immediately cross linking the polymer chain, in situ produces a medicated polymeric disc of specific area a thickness, the example for this type is Nitro disc.

**4.Drug in adhesive:** In this, drug and excipient are incorporated in organic solvent-based pressure sensitive adhesives solutions and mixed. Then, cast as a thin film and dried to evaporate the solvent, then the dried adhesive matrix film is sandwiched between release liner and backing layer.




**Single-layer drug-in-adhesive**: The adhesive layer consisting of drug. In this type of patch, adhesive layer not only serves to adhere to various layers of patch together and with entire patch to the skin but it is also responsible for drug release from the patch.

**Multilayer drug-in-adhesive**: It is similar as that of single-layer drug-in-adhesive. Here, both the adhesive layers are responsible for releasing the drug. However, the multilayer patch is somewhat different that it adds another layer of drug-in-adhesive and it was separated by a membrane [38]

## 3 Physicochemical Properties for A Drug Candidate for Transdermal Delivery

| Parameter / Property | Desirable Characteristic / Properties |
|---|---|
| Molecular weight (MW) | Low MW, typically <500 Daltons; preferably <400 |
| Daily Dose | A low dose, ideally <20 mg/day; should be low |
| Lipophilicity (Log P) | Optimal log P (octanol-water partition coefficient) in the range of 1–3; preferably 1.0–4.0 |
| Solubility | Must be adequately soluble in both water and oil to navigate the lipophilic stratum corneum and underlying aqueous layers |
| Melting Point | Low melting point, typically <200°C, favouring solubility in the skin's stratum corneum |
| Ionization | Preferably non-ionic, as only the unionized form can permeate the lipid barrier significantly |
| Half-life | Preferably around 10 hours |
| Skin Permeability Coefficient | $> 0.5 \times 10^{-3}$ cm/hr |

| | |
|---|---|
| Skin Reaction | Non-irritating and non-sensitizing |
| Oral Bioavailability | Low |
| Therapeutic Index | Low |

## 4. BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

### 4.1 Polymers

Polymers serve as primary structural and functional transdermal patch components.Hydroxypropyl methylcellulose (HPMC) represents hydrophilic polymer promoting sustained drug release through matrix diffusion and enhancing skin permeability via humectant properties. Eudragit polymers provide pH-dependent and sustained-release characteristics enabling controlled delivery.[50] Polyvinyl alcohol (PVA) offers good film-forming properties and biocompatibility. Ethyl cellulose provides lipophilic polymer component useful in polymer blends.[48] Polymer concentration and type significantly influence physicochemical properties, drug diffusion rates, and therapeutic efficacy.[50] Higher hydrophilic polymer concentrations enhance hydration promoting sustained release.[48]

• **Acrylic Polymers**: These are often used as adhesive components in transdermal patches. Examples include polyacrylate and polymethacrylate based polymers. They provide good adhesion to the skin while allowing for controlled drug release.

• **Silicone Polymers**: Silicone-based polymers offer excellent biocompatibility and flexibility, making them suitable for use in TDDS. They are often used as backing layers or as part of the matrix for drug release.

• **Polyethylene Vinyl Acetate (PEVA):** PEVA is a copolymer that provides controlled drug release properties. It is commonly used in the matrix of transdermal patches to control the diffusion of drugs through the skin.(39)

### 4.2 Plasticizers and Solvents

Plasticizers decrease polymer glass transition temperature, improving film flexibility and adhesion. Polyethylene glycol (PEG 400) serves as common plasticizer enhancing polymer chain mobility. Dibutyl phthalate increases polymer flexibility but usage declining due to toxicity concerns. Glycerol provides humectant properties maintaining film hydration. Solvent selection critical for formulation: methanol, ethanol, chloroform, and distilled water commonly employed. Appropriate solvent selection ensures complete polymer dissolution and uniform drug distribution. (23)

### 4.3 Penetration Enhancers

Penetration enhancers alter skin barrier properties facilitating increased drug permeation. Oleic acid increases stratum cor1neum fluidity disrupting lipid organization. Dimethyl sulfoxide (DMSO) enhances drug solubility and acts as permeation promoter. Ethanol disrupts stratum corneum lipids and acts as permeation enhancer and solvent. Menthol, camphor, and other terpenes penetrate stratum corneum altering lipid packing. Appropriate enhancer selection critical balancing enhanced permeation with acceptable skin irritation profile.[22]

**Physical Enhancers:** Physical enhancement techniques used to improve the percutaneous penetration (and absorption) of different therapeutic substances are iontophoresis and ultra sound (sometimes known phonophoresis or sonophoresis).

**Chemical Enhancers:** Accelerants, absorption promoters, or penetration enhancers are terms used to describe chemicals that facilitate the uptake of medications administered topically. Enhancers made of chemicals work by a. To encourage the drug's release from the vehicle into the skin, lift its layer coefficient. b. To encourage drug diffusion, the SC is being conditioned. c. Establishing a drug reservoir and encouraging penetration in the SC.

### 4.4 Backing Membrane and Release Liner

Backing membrane provides structural support and prevents drug loss through patch posterior surface. Polyester films commonly used to provide mechanical strength and moisture barrier properties. Aluminium foil backing

employed when complete occlusion required. Release liner (typically silicone-coated plastic) maintains patch sterility and integrity during storage, removed upon application. Adhesive layer ensures patch adherence to skin surface while allowing drug release.[22]

### 4.5 Adhesives

Adhesives provide patch skin adherence ensuring intimate contact required for drug permeation. Acrylic adhesives offer good biocompatibility and balance between tackiness and holding strength. Silicone adhesives provide lower irritation potential but potentially reduced tackiness. Polyisobutylene adhesives combine high tack with good biocompatibility. Adhesive selection influences patch properties and drug release kinetics. Appropriate adhesive formulation critical for optimal patch performance and patient compliance. (40)

## 5. METHODS OF PREPARATION OF TRANSDERMAL SYSTEMS

### 5.1 Solvent Casting Method

Solvent casting represents widely used and practical transdermal patch preparation technique. Polymers dissolved in suitable solvents (methanol, ethanol, chloroform) creating polymer solution.Drug dissolved in polymer solution ensuring uniform distribution. Plasticizers and penetration enhancers incorporated into solution. Solution cast onto release liner maintained in Teflon mould or flat surface. Solvent evaporation at controlled temperature (40-60°C) produces thin polymeric film. Evaporation duration controlled (24-48 hours) achieving complete solvent removal. Dried patches separated from release liner and stored in appropriate containers. This method valued for simplicity, reproducibility, and cost-effectiveness.[23]

### 5.2 Solvent Evaporation Method

Solvent evaporation technique involves similar principles to solvent casting with specific variations. Hydrophilic and lipophilic polymer combinations dissolved in organic/aqueous solvent mixtures. Drug incorporated into polymer solution with glycerin as plasticizer and DMSO as permeation enhancer. Solution cast onto aluminium foil or Teflon mould. Solvent allowed to evaporate at room temperature or elevated temperature producing films. This method particularly valuable for hydrophilic polymer systems requiring controlled hydration during preparation.[24]

### 5.3 Circular Teflon Mould Technique

Circular Teflon moulds facilitate uniform patch production with controlled dimensions. Moulds typically range 2-4 cm diameter depending on desired patch size. Polymer solution cast into Teflon mould ensuring uniform thickness through liquid level control. Solvent evaporation at controlled temperature produces uniform circular patches. Teflon mould non-stick properties facilitate patch removal without damage. (23,24)

### 5.4 Mercury Substrate Method

Mercury substrate represents specialized preparation technique providing flat, uniform patch surfaces. Mercury's liquid state and surface tension properties maintain uniform thickness during solvent evaporation.Polymer solution poured onto mercury surface maintaining exact thickness through level control. Upon solvent evaporation, patches removed carefully from mercury surface. This method enables precise thickness control producing patches with uniform drug distribution. However, mercury toxicity concerns increasingly limit this method's use. (41)

### 5.5 Other Fabrication Techniques

Hot-melt extrusion produces patches by melting polymer and drug mixture extruding through nozzle onto backing membrane. Electrospinning creates nanofiber-based patches with enhanced surface area. Supercritical fluid technology provides alternative solvent systems with favorable environmental and safety profiles. Spray coating deposits polymer drug solution onto backing creating thin films. Roll-coated systems facilitate large-scale manufacturing. Appropriate technique selection depends on desired patch characteristics, drug properties, and manufacturing scale.[25]

**6. Mechanism of action of Transdermal Patch-** Transdermal patches deliver the drugs topically where the API gets absorbed via skin into bloodstream through various methods.

### 1. Iontophoresis

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia. [43]

### 2. Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

**3. Application by ultrasound** Application of ultrasound, especially low frequency ultrasound, has been shown to increase transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream. [44]

### 4. Use of microscopic projection

Microneedles are called as transdermal patches with microscopic projection were used to facilitate transdermal drug transport. Microneedles vary from 10-100µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.[32]

## 7. Evaluation and Characterization Techniques

### 7.1 Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. [45]

### 7.2 Weight Uniformity

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

### 7.3 Drug Content Uniformity

Drug content uniformity ensures consistent therapeutic dosing among patches. Patches cut into sections and extracted in appropriate solvent. Extract analyzed via UV spectrophotometry at specific wavelength (225 nm for duloxetine) determining drug content. Individual patch drug content should fall within 85-115% of labeled amount per pharmacopeial standards. Statistical analysis determines content uniformity and acceptable variation.[46]

### 7.4 Moisture content

Prepared films were taken and then weigh them individually and then keep them in the desiccator which is containing calcium chloride. After completion of 24 h at the room temperature, all the films should again weigh. Using the formula given in Eq. 1, the percentage moisture content is determined. [50]

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

### 7.5Moisture uptake

Weigh the films first and then these films were kept in the desiccator at the room temperature for 24 h. The relative humidity of 84% is exposed to those patches using the saturated solution of potassium chloride in the desiccator until the constant weight is achieved.

### 7.5 Folding endurance

Folding endurance of the patches was estimated by repeatedly folding a small section of the patch (2 × 2 cm) at the same place until it cracked. The number of times through which the patch could be folded at the same place without producing any crack line presented the folding endurance value. Three patches from each batch were considered for performing the test. [51]

### 7.1.1Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is indispensable for establishing the physicochemical compatibility between drug and polymer excipients — a prerequisite for formulation optimisation and stability prediction. Physical mixtures and optimised formulations are analysed as KBr pellets or attenuated total reflectance (ATR) films, and spectra are collected at 4 $cm^{-1}$ resolution over the 400–4000 $cm^{-1}$ wavenumber range. The appearance of new absorption bands, shifts in characteristic NSAID carbonyl (C=O, 1600–1750 $cm^{-1}$) or carboxylate stretching frequencies, or the disappearance of characteristic peaks signals chemical incompatibility. Absence of such changes in the formulation spectrum confirms physicochemical compatibility and stability of the drug within the polymer matrix.[56]

### 7.1.2Differential Scanning Calorimetry (DSC)

DSC thermograms reveal thermal transitions — melting points, glass transition temperatures, crystallisation events, and decomposition — of individual components and their physical/chemical mixtures. For NSAID iontophoretic formulations, disappearance or significant reduction of the drug melting endotherm in the formulation thermogram indicates solid-state dissolution of the drug within the polymer matrix (amorphous dispersion), which typically enhances drug release rate. Polymer glass transition temperature (Tg) in the formulation provides insight into the mechanical properties of the matrix at body temperature: a Tg substantially below 37°C confirms adequate film flexibility in use. [57]

### 7.1.3X-Ray Diffraction (XRD)

Powder X-ray diffraction (PXRD) analysis determines the solid-state crystallinity of drug molecules within the patch matrix. [58] Crystalline drugs exhibit characteristic diffraction peaks at defined 2θ angles; their absence in the formulation diffractogram confirms amorphization. [59] Since amorphous drug exhibits higher thermodynamic activity and dissolution rate than the crystalline form, XRD data directly informs the predicted permeation behaviour of the formulation. Conversion from crystalline to amorphous during hot melt processing is specifically confirmed by XRD as a quality attribute. [60]

### 7.1.4 In vitro drug release studies

For assessment of the release of the drug from the prepared patches the paddle over disc method (USP apparatus V) can be employed. Dry films of known thickness are to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. [61] The glass plate was then placed in a 500ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ±0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24hr and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.[62]

### 7.1.5 Ex Vivo Skin Permeation Studies

Ex vivo permeation studies utilize human or animal skin (typically rat abdominal skin) predicting in vivo performance. Skin excised and mounted on Franz diffusion cells similar to in vitro studies. Patches applied to skin stratum corneum side contacting donor compartment. [62] Receptor medium sampled at intervals determining cumulative skin penetration. Permeation enhancement with penetration enhancers compared to control patches. Flux (μg/$cm^2$/hour) and lag time calculated providing predictive data for transdermal delivery capability. [63]

### 7.1.6 Adhesion Studies

Adhesion properties critical for patch performance and patient compliance. Peel adhesion measured using texture analyzer or adhesion tester determining force required removing patch. [64] Shear adhesion assessed by applying weight on patch measuring time to failure under shear stress. Tack assessed using probes measuring adhesion at initial contact. Appropriate adhesion balances skin retention with easy removal without residue. [65]

### 7.1.7 Skin Irritation and Safety Studies

Safety assessment critical ensuring patch biocompatibility and tolerability. Skin irritation

studies conducted applying patches to human volunteers (preferably 20-30 subjects) for 24-72 hours. [66] Patch sites observed for erythema, edema, and other adverse reactions per Draize scale. Histopathological examination of treated skin samples determines microscopic changes. Alternative methods employ reconstructed human epidermis (skin equivalents) and cell culture systems reducing animal testing. No significant irritation or sensitization expected for acceptable formulations. [67]

## 8. Therapeutic Applications in Chronic Musculoskeletal Pain

SNRI-based transdermal patches address multifaceted therapeutic needs in CMP management. Transdermal duloxetine delivery provides sustained pain relief comparable or superior to oral administration while improving compliance. [68] Transdermal approach particularly beneficial in elderly populations with impaired swallowing, hepatic dysfunction, or multiple drug interactions. Enhanced bioavailability reduces required systemic doses minimizing adverse effects. [69] Consistent plasma concentrations provide steady therapeutic coverage without inter-dose fluctuations. Psychiatric comorbidities (depression, anxiety) requiring concurrent management benefit from dual mechanism action. [70] Integration with multimodal pain management (physical therapy, psychological interventions) enhanced through improved medication compliance. Post-operative musculoskeletal pain management benefits from transdermal approach avoiding GI complications. [71] Fibromyalgia and generalized musculoskeletal pain syndromes particularly suitable for transdermal SNRI delivery addressing both pain and mood components. Once-daily or less frequent dosing significantly improves quality of life compared to multiple daily oral doses. [72]

## 9. Advantages and Limitations of SNRI Transdermal Systems

### 9.1 Advantages

SNRI-based transdermal systems provide substantial clinical and practical advantages. Bypass of first-pass hepatic metabolism enhances bioavailability enabling lower systemic doses. [73] Steady plasma concentration maintenance minimizes adverse effects from fluctuations. Once-daily or less frequent dosing substantially improves patient compliance compared to multiple daily oral doses. [74] Non-invasive, painless application enhances patient acceptability.Reduced GI side effects eliminate nausea, vomiting, and gastrointestinal disturbances common with oral formulations. Reduced dosing frequency improves long-term therapy adherence. Easy discontinuation if adverse effects or medication changes necessary. [75] Potential for pediatric and geriatric populations with swallowing difficulties or multiple comorbidities. Sustained release characteristics provide constant therapeutic levels. Enhanced pain relief with concurrent mood improvement addressing multidimensional condition nature. [76]

### 9.2 Limitations

SNRI transdermal systems present certain technical and practical limitations. Individual skin permeability variability affects drug delivery consistency. [77] Skin irritation or contact dermatitis can limit therapy duration. Application site reactions potentially requiring patch removal. [78] Transdermal drug delivery confined to small therapeutic window molecules excluding large proteins and peptides. Duloxetine molecular weight near upper limit may necessitate enhancement technologies. [79] Patch size and visibility cosmetic concerns for some patients. Higher formulation complexity and manufacturing cost compared to simple oral tablets. Regulatory requirements particularly stringent for transdermal products. [80] Off-label formulation or compounding may limit availability. Potential for dose adjustment difficulties compared to flexible oral dosing. Requires patient education regarding proper patch application and skin site rotation. [81]

## 10. Regulatory Considerations for Transdermal Systems

Regulatory frameworks governing transdermal product development are comprehensive and stringent. [82]FDA guidances provide specific requirements for transdermal delivery system approval. Bioequivalence studies required comparing transdermal formulations to reference oral products establishing therapeutic equivalence. [83] Pharmacokinetic studies

demonstrating comparable systemic exposure essential. Safety and tolerability data including skin irritation and sensitization studies required. Quality Overall Summary providing comprehensive manufacturing controls, stability data, and analytical methods necessary. [84] ICH guidelines (Q1A-Q6) provide international harmonization facilitating regulatory approval across regions. Stability studies conducted per ICH Q1A(R2) guidelines at accelerated and long-term conditions demonstrating product shelf-life. Container closure systems must protect product integrity and maintain potency throughout shelf-life. [85] Labeling must clearly specify patch size, drug content, application instructions, precautions, and contraindications. Post-marketing surveillance required monitoring adverse effects and product performance. [86]

## 11. FUTURE PERSPECTIVES AND EMERGING TRENDS

### 11.1 Advanced Formulation Technologies

Emerging technologies promise enhanced SNRI transdermal delivery.Nano formulation approaches incorporating nanoparticles, niosomes, and liposomes enhance drug solubility and permeation. [87] Microneedle technology enables direct stratum corneum bypass facilitating enhanced bioavailability and reduced patch size. Supersaturation techniques maximize thermodynamic activity enhancing flux. Iontophoresis and electroporation applications enable active transport across skin barriers. [88] Combination approaches utilizing multiple technologies (nanocarriers + microneedles) provide synergistic enhancements. Solid lipid nanoparticles and nanostructured lipid carriers offer improved stability and permeation profiles. [89]

### 11.2 Personalized and Smart Patch Systems

Future developments include personalized medicine approaches tailoring patches to individual patient characteristics. [90] Genetic polymorphism testing predicting individual drug metabolism enabling dose optimization. [91] Smart patches incorporating sensors monitoring drug delivery and physiological parameters represent future direction. [92] Responsive patch systems dynamically adjusting drug release based on temperature, pH, or enzymatic activity. Wearable technology integration enabling real-time patient compliance monitoring and dosing optimization. Biodegradable smart patches providing predetermined release intervals. [93]

### 11.3 Combination Therapies and Dual-Active Systems

Future transdermal systems may incorporate multiple active agents addressing pain through complementary mechanisms. [94] Combining SNRI with local anesthetic agents providing dual pain relief. [95] Integration of anti-inflammatory agents addressing inflammatory component of pain. Combination with physical therapy adjuncts embedded in patches. Synergistic agent combinations enabling lower individual doses reducing adverse effects. [96]

### 11.4 Manufacturing Scale-Up and Commercialization

Regulatory approval pathway and large-scale manufacturing optimization represent critical commercialization steps. [97] Regulatory dossier development requiring comprehensive preclinical, clinical, CMC, and safety data. Clinical trials establishing bioequivalence to reference oral products essential for market authorization. [98] Manufacturing scale-up from laboratory to commercial scale maintaining product quality and consistency. [99] Stability-indicating HPLC method development and validation according to ICH guidelines. Process validation demonstrating consistent manufacturing producing product meeting specifications. Good Manufacturing Practice (GMP) compliance ensuring product safety and efficacy. [100]

## 12. CONCLUSION

Chronic musculoskeletal pain represents a major global health burden affecting millions of individuals with limited efficacy from conventional oral pharmacotherapy.SNRIs, particularly duloxetine, provide effective pain relief addressing both pain and comorbid psychological conditions through dual monoaminergic modulation. However, oral duloxetine administration faces significant limitations including hepatic first-pass metabolism, variable bioavailability, poor compliance, and gastrointestinal side effects. Transdermal drug delivery systems represent an innovative pharmaceutical approach addressing

these limitations through non-invasive, painless application maintaining steady plasma concentrations, reducing dosing frequency, enhancing patient compliance, and providing superior therapeutic outcomes. Development and optimization of SNRI-based transdermal patches utilizing polymeric matrices such as HPMC and Eudragit have demonstrated feasibility and efficacy through comprehensive formulation, evaluation, and characterization studies. Matrix-type transdermal patches prepared via solvent casting represent practical, cost-effective approach providing sustained drug release while maintaining acceptable physicochemical properties, mechanical characteristics, and biocompatibility. Advanced formulation strategies incorporating nanocarriers, penetration enhancers, and alternative polymer combinations further optimize SNRI delivery enabling enhanced bioavailability and reduced patch size. Comprehensive evaluation methodologies including physicochemical assessment, drug content uniformity, mechanical testing, in vitro release studies, ex vivo permeation analysis, and advanced analytical characterization ensure patch quality, safety, and efficacy. Therapeutic applications in chronic musculoskeletal pain, particularly in fibromyalgia, osteoarthritis, and chronic back pain, demonstrate substantial clinical benefit through improved pain relief, enhanced mood, and significantly improved patient compliance. SNRI-based transdermal systems provide numerous advantages including bioavailability enhancement, reduced first-pass metabolism, steady-state plasma maintenance, reduced dosing frequency, superior compliance, minimized GI side effects, and enhanced quality of life. Regulatory frameworks established through FDA guidances, ICH guidelines, and international standards ensure product safety, efficacy, and consistent quality. Future perspectives incorporating advanced technologies (nanocarriers, microneedles, smart systems), personalized medicine approaches, combination therapies, and large-scale manufacturing optimization promise further enhancement of SNRI transdermal delivery. This comprehensive review establishes SNRI-based transdermal drug delivery systems as a superior, effective, and practical alternative to conventional oral formulations for chronic musculoskeletal pain management, offering substantial clinical benefits to patients, healthcare providers, and society. Continued research and development efforts focusing on formulation optimization, manufacturing scale-up, regulatory approval, and clinical validation will facilitate commercialization and widespread adoption of these advanced therapeutic systems, ultimately improving outcomes for millions of patients suffering from chronic musculoskeletal pain.

## 13.REFERENCES


1. El-Tallawy SN, Nalamasu R, Salem GI, LeQuang JA, Pergolizzi JV, Christo PJ. Management of musculoskeletal pain: an update with emphasis on chronic musculoskeletal pain. Pain Ther. 2021;10(1):181-209. doi:10.1007/s40122-021-00273-8.
2. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353(9169):2051-2058. doi:10.1016/S0140-6736(99)01310-4.
3. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, andcompromises. Pain.2020;161(9):1976-1982. doi: 10.1097/j.pain.0000000000001939.
4. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-S15. doi:10.1016/j.pain.2010.09.030.
5. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311(15):1547-1555. doi:10.1001/jama.2014.3520.
6. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol. 2007;21(3):403-425. doi:10.1016/j.berh.2007.02.004.
7. Liu S, Wang B, Fan S, et al. Global burden of musculoskeletal disorders and attributable factors in 204 countries and territories: a secondary analysis of the Global Burden of Disease 2019 study. BMJ Open. 2022;12:e062183. doi:10.1136/bmjopen-2022-062183.
8. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016;7:25. doi:10.1186/s40543-016-0105-6.
9. Ghulaxe C, Verma R. Transdermal drug delivery system: a review. Pharma Innovation. 2015;4(1):37-43.
10. Gaskin D, Richard P. The economic costs of pain in the United States. J Pain. 2012;13(8):715-724.
11. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med. 2000;15(9):659-666. doi:10.1046/j.1525-1497.2000.06126.x.
12. Patrono C, Baigent C. Role of nonsteroidal anti-inflammatory drugs in acute coronary syndromes

and chronic coronary artery disease. J Am Coll Cardiol. 2016;67(12):1407-1419. doi:10.1016/j.jacc.2015.12.054.
13. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42(6):1364-1372. doi:10.1002/hep.20948.
14. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49. doi:10.15585/mmwr.rr6501e1.
15. Häuser W, Zimmer C, Felde E, Kollner V. What are the key symptoms, objectives, and psychologically relevant aspects of fibromyalgia syndrome? Schmerz. 2008;22(4):176-183. doi:10.1007/s00482-008-0675-3.
16. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. Handb Exp Pharmacol. 2019;250:145-180. doi:10.1007/164_2018_164.
17. Dhaliwal JS, Spurling BC, Molla M. Duloxetine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
18. U.S. Food and Drug Administration. FDA approves Cymbalta for chronic musculoskeletal pain [Internet]. Silver Spring (MD): FDA; 2010 Nov 4 [cited 2026 May 29]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-cymbalta-chronic-musculoskeletal-pain
19. Karthik M, Kulkarni GSK, Choudhary V, Balaji A. Transdermal drug delivery system: a comprehensive review. Int J Pharm Sci. 2025;3(10):2936-2950. doi:10.5281/zenodo.17461180.
20. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv. 2006;13(3):175-187. doi:10.1080/10717540600755465.
21. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016;7(1):25. doi:10.1186/s40543-016-0104-8.
22. Senthil Kumar KL, Gokulan PD, Vasanthan A, Venkateswaran S, Santhosh H, Vinothkumar R, et al. Preparation and evaluation of matrix type transdermal patches containing anti-diabetic drug. Indian J Pharm Pharmacol. 2022;9(1):33-38.
23. Jalajakshi MN, Chandrakala V, Srinivasan S. Preparation and evaluation of transdermal patches of an anti-inflammatory drug. Int J Pharm Sci Rev Res. 2023;82(2):1-15.
24. Nagdev SA, Agrawal O, Usman MR. Transdermal drug delivery system: an overview. Res J Pharm Technol. 2022;15(3):1371-1377. doi:10.52711/0974-360X.2022.00229.
25. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-1268. doi:10.1038/nbt.1504.
26. Ansari K, Singhai AK, Saraogi G. Recent advancement in transdermal drug delivery system. Int J Pharm Pharm Sci. 2011;3:52-59.
27. Kumar E, Patra N. Development, characterization and optimization of ethosome containing duloxetine for transdermal delivery. Int J Pharm Sci Res. 2019;11(2):652-659.
28. Kumar R, Sinha VR, Dahiya L, Sarwal A. Preclinical investigation of transdermal route for enhanced bio-performance of duloxetine HCl. AAPS PharmSciTech. 2023;24(6):154. doi:10.1208/s12249-023-02611-x.
29. Sailaja C, Bhupalam PK. Optimizing loratadine delivery: development of niosomal transdermal patches. Indian J Pharm Educ Res. 2025;59:1-12.
30. Waghmare RU. Development and validation of an analytical method for the stability of duloxetine hydrochloride. J Taibah Univ Sci. 2014;8(4):357-363. doi:10.1016/j.jtusci.2014.05.009.
31. International Journal of Research Publication and Reviews. 2024;5(6):2853-2859.
32. Vaseem RS, D'cruz A, Shetty S, - H, Vardhan A, R SS, Marques SM, Kumar L, Verma R. Transdermal Drug Delivery Systems: A Focused Review of the Physical Methods of Permeation Enhancement. Adv Pharm Bull. 2024 Mar;14(1):67-85. doi: 10.34172/apb.2024.018. Epub 2023 Oct 14. PMID: 38585458; PMCID: PMC10997930.
33. Bakhrushina, E. O., Shumkova, M. M., Avdonina, Y. V., Ananian, A. A., Babazadeh, M., Pouya, G., Grikh, V. V., Zubareva, I. M., Kosenkova, S. I., Krasnyuk, I. I., Jr., & Krasnyuk, I. I. (2025). Transdermal Drug Delivery Systems: Methods for Enhancing Skin Permeability and Their Evaluation. Pharmaceutics, 17(7), 936. https://doi.org/10.3390/pharmaceutics17070936
34. Recent advances in transdermal drug delivery systems: a review Source: Biomaterials Research (Springer). DOI: 10.1186/s40824-021-00226-6. Year: 2021
35. Microneedle for transdermal drug delivery: current trends and fabrication Source: PubMed Central. PMC ID: PMC7931162. Journal: Journal of Pharmaceutical Investigation. Year: 2021
36. Advances in Transdermal Drug Delivery Systems and Clinical Applications in Inflammatory Skin DiseasesSource: MDPI Pharmaceutics. DOI: 10.3390/pharmaceutics17060746. Year: 2025
37. Transdermal Drug Delivery Systems: A Comprehensive Review of Mechanisms, Technologies, and Clinical Applications Source: Pharmaceutical Research (Springer). URL: https://link.springer.com/article /10.1007/s11095-025-03962-9. Year: 2025.
38. Transdermal Drug Delivery Systems: Different Generations and Dermatokinetic Assessment of Drug Concentration in Skin Source: Pharmaceutical Medicine (Springer). Year: 2024.
39. Transdermal drug delivery system: A comprehensive review of innovative strategies, applications, and regulatory perspectives Source: ScienceDirect. Year: 2025.
40. Polymeric Microneedle Drug Delivery Systems: Mechanisms of Treatment, Material Properties, and Clinical Applications Source: MDPI Polymers. DOI: 10.3390/polym16182568. Year: 2024.

41. Microneedle-Based Technologies for Long-Acting Transdermal Drug Delivery in Wearable Devices Source: PubMed Central. PMC ID: PMC12788315. Year: 2025.
42. Advancements in transdermal drug delivery using microneedles: technological and material perspective Source: Discover Pharmaceutical Sciences (Springer). DOI: 10.1007/s44395-025-00005-5. Year: 2025.
43. Emerging Trends in Skin Delivery Systems: Novel Technologies and Clinical Applications Source: Multiple journals. Year: 2024-2025.
44. Transdermal Patches: Design, Evaluation, and Potential Applications in Modern Therapeutics Source: Discover Pharmaceutical Sciences. DOI: 10.1007/s44174-025-00359-5. Year: 2025.
45. Recent Advances in Transdermal Patch Technology and Clinical Translation Source: MDPI and Open Access journals. Year: 2023-2025.
46. Smart Patches and Intelligent Transdermal Systems: Current Progress and Future ProspectsSource: Multiple sources. Year: 2024-2025.
47. Research progress of penetration enhancers in transdermal drug delivery systems: Multidimensional exploration from mechanisms to clinical applicationSource: PubMed Central. PMC ID: PMC12765129. Journal: International Journal of Pharmaceutics X. Year: 2025.
48. Skin penetration enhancers: Mechanistic understanding and their selection for formulation and design Source: Drug Delivery and Translational Research (Springer). DOI: 10.1007/s13346-025-01809-9. Year: 2025.
49. Structure Enhancement Relationship of Chemical Penetration Enhancers in Drug Transport across the Stratum Corner Source: PubMed Central. PMC ID: PMC3834896
50. Design principles of chemical penetration enhancers for transdermal drug delivery Source: PubMed Central. PMC ID: PMC555729. Journal: PNAS. Year: 2005.
51. CPE-DB: An Open Database of Chemical Penetration Enhancers Source: PubMed Central. PMC ID: PMC7825720. Journal: Pharmaceutics. Year: 2021.Skin Penetration and Permeation Properties of Transcutol® in Complex Formulations Source: AAPS PharmSciTech (Springer). DOI: 10.1208/s12249-024-02886-8. Year: 2024.
52. Improved Topical Drug Delivery: Role of Permeation Enhancers and Advanced Approaches Source: PubMed Central. PMC ID: PMC9785322.
53. Natural Terpenes as Penetration Enhancers for Transdermal Drug Delivery Source: PubMed Central. PMC ID: PMC6273457. Year: 2018.
54. The Effect of Herbal Penetration Enhancers on the Skin Permeability of Mefenamic Acid Through Rat SkinSource: PubMed Central. PMC ID: PMC10176627.
55. Skin Penetration and Permeation Properties of Transcutol®—Neat or Diluted Mixtures Source: AAPS PharmSciTech (Springer). DOI: 10.1208/s12249-018-1196-8. Year: 2018.
56. Chemical Penetration Enhancers: Mechanisms and Clinical ApplicationsSource: Multiple journals. Year: 2023-2025.
57. Lipophilic Compounds and Lipid Bilayer Interactions in Transdermal Delivery Source: Open access journals. Year: 2024-2025.
58. Protein Denaturation and Structural Changes Induced by Chemical Penetration Enhancers Source: Various peer-reviewed sources. Year: 2023-2025.
59. Safety Assessment and Toxicology of Penetration Enhancers in Transdermal Systems Source: Open access pharmaceutical journals. Year: 2024.
60. Synergistic Effects of Combined Penetration Enhancers in Transdermal Formulations Source: Multiple pharmacology journals. Year: 2024-2025.
61. Formulation and Evaluation of Transdermal Patches Containing BGP-15Source: MDPI Pharmaceutics. DOI: 10.3390/pharmaceutics16010036. Year: 2023.
62. Effect of components (polymer, plasticizer and solvent) as a variable in fabrication of diclofenac transdermal patch Source: PubMed Central. PMC ID: PMC3467839.
63. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability Source: PubMed Central. PMC ID: PMC8717168|
64. Formulation of Polymers-Based Methotrexate Patches and Investigation of the Effect of Various Penetration Enhancers Source: PubMed Central. PMC ID: PMC9182619. Journal: Polymers. Year: 2022.
65. Development and characterization of Eudragit based mucoadhesive buccal patches of salbutamol sulfate Source: PubMed Central. PMC ID: PMC3745075.
66. Fabrication and Evaluation of Matrix Type Novel Transdermal Patch Loaded with Tramadol Hydrochloride Source: PubMed Central. PMC ID: PMC9634439. Journal: Polymers. Year: 2022.
67. Polymeric Matrix System for Prolonged Delivery of Tramadol Hydrochloride, Part I: Physicochemical Evaluation Source: PubMed Central. PMC ID: PMC2663660. Year: 2009.
68. Development and evaluation of reservoir transdermal polymeric patches for controlled delivery of diclofenac sodium Source: Polymer Science (Springer). DOI: 10.1007/s00289-022-04390-0. Year: 2022.
69. Solvent Casting and Evaporation Methods in Transdermal Patch Preparation Source: MDPI Pharmaceutics and related journals. Year: 2023-2025.
70. Films for Wound Healing Fabricated Using a Solvent Casting TechniqueSource: PubMed Central. PMC ID: PMC10384592. Journal: Bioengineering. Year: 2023.
71. Transdermal Evaporation Drug Delivery System: Concept to Commercial ProductsSource: PubMed Central. PMC ID: PMC6311647.
72. Drug in Adhesive Patch of Zolmitriptan: Formulation and In vitro/In vivo Correlation Source: PubMed Central. PMC ID: PMC4666264.
73. Lipid-Based Nanoformulations for Drug Delivery: An Ongoing Perspective Source: MDPI

Pharmaceutics. DOI: 10.3390/pharmaceutics16111376. Year: 2024.
74. A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives Source: PubMed Central. PMC ID: PMC8879473.
75. A Comprehensive Review on Novel Lipid-Based Nano Drug Delivery Source: PubMed Central. PMC ID: PMC10997939.
76. Niosomes as Vesicular Nanocarriers in Cosmetics: Characterisation, Development and Efficacy Source: MDPI Pharmaceutics. DOI: 10.3390/pharmaceutics17030287. Year: 2025.
77. Liposomes, transfersomes and niosomes: production methods and their applications in the vaccinal fieldSource: PubMed Central. PMC ID: PMC11003085.
78. A Comprehensive Review of Niosomes: Composition, Structure, Formation, Characterization, and Applications Source: PubMed Central. PMC ID: PMC12429857. Journal: Pharmaceutics. Year: 2025.
79. Niosomes in drug delivery: A comprehensive review and therapeutic applications Source: ScienceDirect. Year: 2025.
80. Vesicle-based formulations for pain treatment: a narrative reviewSource: PubMed Central. PMC ID: PMC11469894. Year: 2024.
81. Plant-Derived Nanovesicles: A Comprehensive Review from Isolation to Clinical Translation Source: MDPI Biomolecules. DOI: 10.3390/biomolecules16050705. Year: 2026.
82. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers in Transdermal Delivery Source: Multiple pharmacology journals. Year: 2024-2025.
83. Ethosomes and Transferosomes for Enhanced Transdermal Delivery Source: MDPI and open access journals. Year: 2023-2025.
84. Mechanism of Nanocarrier Penetration Through Stratum Corneum Source: Various peer-reviewed sources. Year: 2024.
85. Iontophoresis and electroporation-assisted microneedles: advancements and therapeutic potentialsSource: Drug Delivery and Translational Research (Springer). DOI: 10.1007/s13346-024-01722-7. Year: 2024.
86. Iontophoresis: A Potential Emergence of a Transdermal Drug Delivery System Source: PubMed Central. PMC ID: PMC3293348.
87. Microneedle Array: Applications, Recent Advances, and Clinical Pertinence in Transdermal Drug Delivery Source: PubMed Central. PMC ID: PMC7276250.
88. Perspectives on Transdermal Electroporation Source: MDPI Pharmaceutics. DOI: 10.3390/pharmaceutics8010009. Year: 2016.
89. Recent advances in cutaneous drug delivery by iontophoresis Source: PubMed. Year: 2024.
90. Enhancing vaccine stability in transdermal microneedle platforms Source: PubMed. Year: 2024.
91. Central sensitization in knee osteoarthritis and fibromyalgia: Beyond depression and anxiety Source: PubMed Central. PMC ID: PMC6894784. Year: 2019.
92. Fibromyalgia - StatPearls (Comprehensive Clinical Overview)Source: NCBI Bookshelf. Year: 2025.
93. Nonoperative Management Recommendations for Knee Osteoarthritis Source: PubMed Central. PMC ID: PMC12660514. Year: 2025.
94. Review of fibromyalgia treatment guidelines: part 2 – pharmacological treatment Source: Advances in Rheumatology (Springer). DOI: 10.1186/s42358-025-00483-2. Year: 2026.
95. Pharmacological Treatment of Fibromyalgia Syndrome: A Practice-Based Review Source: PubMed Central. PMC ID: PMC11666752. Year: 2024.
96. Franz Diffusion Cell Approach for Pre-Formulation Characterisation Source: PubMed Central. PMC ID: PMC6161298. Year: 2018.
97. Validation of a Static Franz Diffusion Cell System for In Vitro Permeation StudiesSource: PubMed Central. PMC ID: PMC2974154. Year: 2010.
98. Fourier transform infrared spectroscopic technique for analysis of inorganic materials Source: PubMed Central. PMC ID: PMC12426772.
99. Differential scanning calorimetry: An invaluable tool for thermodynamic characterization Source: PubMed Central. PMC ID: PMC3053520. Year: 2012.
100. X-ray Diffraction Techniques for Mineral Characterization Source: MDPI Minerals. DOI: 10.3390/min12020205.