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REVIEW ARTICLE

NOVEL DRUG DELIVERY SYSTEM

CURRENT TRENDS IN NDDS WITH SPECIAL REFERENCE TO NSAIDS

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ABSTRACT

Transdermal drug delivery system has been in existence for a long time. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Non-steroidal anti-inflammatory drugs used as analgesic, anti-inflammatory and antipyretic in the treatment of rheumatoid arthritis and osteoarthritis, but the clinical use is often limited because of adverse effect such as irritation and ulceration of the gastrointestinal tract. These drugs have a relatively short half-life in plasma and have the potential to be delivered topically, it also has low molecular weight. NSAIDs are an excellent drug for transdermal delivery. Furthermore, topical administration via the dermal route can bypass disadvantages of the oral route. Therefore, transdermal drug delivery has been considered to be an ideal route for administration of NSAIDs.

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KEY WORDS

Transdermal, Ketoprofen, NSAIDs, Rheumatoid arthritis

1. INTRODUCTION

Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.

Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting.

An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Novel drug delivery is a vital research area which strives to solve this problem and aim to achieve a programmed delivery of the therapeutic substances for the optimal beneficial effects while avoiding the side effect of drugs. A novel drug delivery system is a system that offers multiple drug delivery solutions such as:

- Oral Drug Delivery Systems and Materials
- Parenteral and Implant Drug Delivery Systems
- Pulmonary and Nasal Drug Delivery
- Transmucosal Drug Delivery
- Transdermal and Topical Drug Delivery
- Delivery of Proteins and Peptides
- Drug Delivery Pipelines[1]

Traditional preparations used include ointments, gels, creams and medicinal plasters containing natural herbs and compounds. Clearly, the clinical benefits, industrial interest, strong market and regulatory precedence show why TDD has become a successful and viable dosage form. The smallest drug molecule presently formulated in a patch is nicotine (162

Da) and the largest is oxybutinin (359 Da). Opening the transdermal route to large hydrophilic drugs is one of the major challenges in the field of TDD. Anatomically, the skin has many histologic layers but in general, it is described in terms of three major tissue layers: the epidermis, the dermis and the hypodermis. The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. Stratum corneum is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out[2].

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at controlled rate to systemic circulation. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the blood stream thus stratum corneum is rate limiting step for permeation of transdermal preparation.

1.1 Percutaneous absorption

The percutaneous absorption of drug in three ways:

- Transdermal absorption
- Transfollicular absorption
- Clearance by local circulation

1.2 *Kinetics of Transdermal Permeation*

Transdermal permeation of the drug involves the following steps;

- Sorption by the stratum corneum
- Penetration of drug through viable epidermis
- Uptake of drug by the capillary network in the dermal papillary layer

The rate of permeation across the skin (dq/dt) is given by:

$$dq/dt = P_s (c_d - c_r) \quad \text{---- (1)}$$

Where c_d and c_r are, the concentration of skin penetrant in the donor compartment (e.g. on the surface of stratum corneum fig1.1) and in the receptor compartment (e.g., body) respectively. P_s is the overall permeability coefficient of the skin tissues to the penetrant. This permeability coefficient is given by the relationship: $P_S = K_s D_{ss} / h_s$ ---- (2)

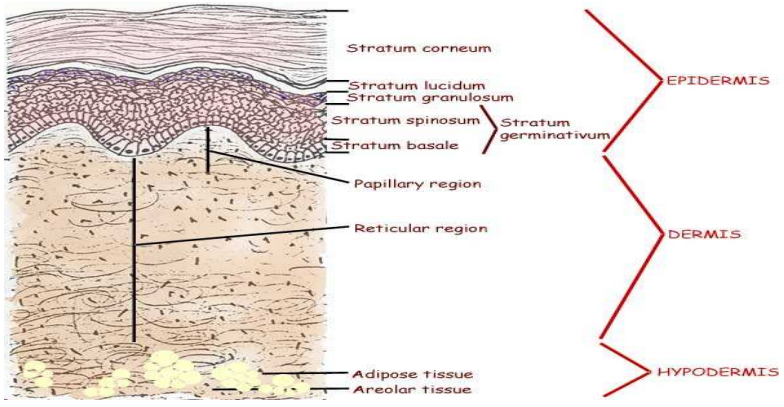

Fig 1.1
Microscopic cross-section view of human skin

where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues. As K_s, D_{ss} and h_s are constant under given conditions, the permeability coefficient (P_s) for a skin penetrant can be considered to be constant. From equation (1) it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneum (C_d) is consistently and substantially greater than the drug concentration in the body (C_r).

Then equation (1) becomes: $dq/dt = P_s C_d$ and the rate of skin permeation (dq/dt) is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a) i.e., $R_r >> R_a$.since R_r is greater than R_a, the drug concentration on the skin surface (C_d) is maintained at a level equal to or greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C_s) i.e., $C_d >> C_s$. Therefore, a maximum rate of skin permeation [(dq/dt_m)] is obtained and is given by the equation: $(dq/dt_m) = P_s C_s$ ------- (4)

From the above equaton, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient (P_s) and its equilibrium solubility in the stratum corneum (C_s). Thus skin permeation appears to be stratum corneum limited. Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum, epidermis, and dermis (fig 1.2). The stratum corneum being keratinized tissue, behaves as a semi-permeable artificial membrane and drug molecules penetrate by passive diffusion.

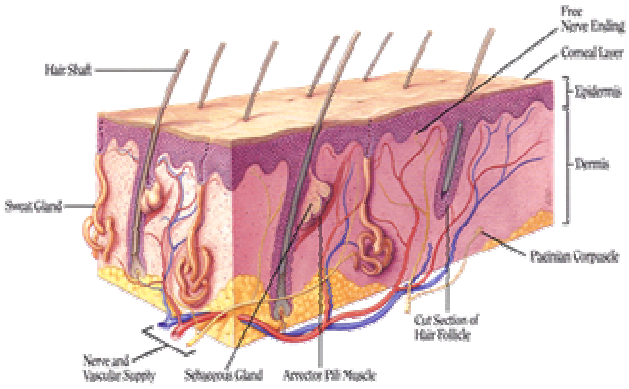

Fig 1.2
Cross-sectional view of human skin

1.3 *Potential Benefits of Transdermal Systems*

- Bypasses the first pass metabolism, avoids inactivation of drugs by pH effects and

enzymes present in GI tract, which otherwise happens on oral administration.
- Provide for multiple daily doses with a single application.
- Provide a means to quickly terminate dosing.
- Provide improved systemic bioavailability of active ingredients.
- Sustains therapeutic drug levels.
- Permits self-administration.
- Non-invasive (no needles or injections).

1.4 *limitations*

- The drug must have desirable physico-chemical properties to penetrate the stratum corneum. Drugs that require high blood levels cannot be administered.
- Skin irritation or contact dermatitis due to use of drugs, excipients, enhancers and adhesives used.
- The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.
- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

1.5 *Formulation component of Transdermal Drug Delivery system*

a. Polymer matrix or matrices.
b. The drug
c. Permeation enhancers
d. Other excipients

a) Polymer Matrix:

Polymer must posses the following properties;

- Mol wt. & chemical functionality should be such that specific drug diffuses properly and gets released through it.
- Stable, non reactive with the drug, easily manufactured and inexpensive.
- Polymer and its degradation products must be non toxic.
- Mechanical properties should not deteriorate excessively when large amounts of active ingredient are incorporated in it.

The types of polymers are:

i) Natural Polymers: e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

ii) Synthetic Elastomers: e.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Neoprene etc.

ii) Synthetic Polymers: e.g. PVA, PVC, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, PVP, Polymethylmethacrylate etc.

b) Drug:

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties of drug

- The drug should have a molecular weight less than 500 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have low melting point.
- The drug should be potent, having short half life and be non irritating.

c) Permeation Enhancers:

These are compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings: - J = D dc/dx.

i) Solvents

These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include:-

a) Water
b) Alcohols – methanol and ethanol;
c) Alkyl Methyl Sulfoxides – dimethyl sulfoxide, alkyl homologes of methyl sulfoxide dimethyl acetamide and dimethyl formamide ;
d) Pyrrolidones – 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone),
e) Miscellaneous Solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

ii) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl ulphoxide etc.

- **Nonionic Surfactants:** e.g. Pluronic F127, Pluronic F68, etc.
- **Bile Salts:** e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
- **Binary system:** These chemicals open up the heterogenous multilaminate pathway as well

The continuous pathways. E.g. Propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid.

iii) Miscellaneous chemicals

These include;

- Urea, a hydrating and keratolytic agent;
- N,N-dimethyl-m-toluamide

Some potential permeation enhancers have recently been investigated but the available data on their effectiveness sparse. These include eucalyptol, di-o-methyl-ß-cyclodextrin and soyabean casein.

d) Other Excipients:

Characteristics:

- Should not cause imbalance in normal skin flora, should not be irritant
- Should adhere skin aggressively during dosing interval
- Should be easily removed
- Should not leave any residue
- Should not affect permeation of drug

Some examples of excipients:

- Poly isobutene
- Acrylics
- Silicones
- Face adhesives
- Peripheral adhesives.

Peripheral adhesive is less elegant, contains several more layers, is substantially larger and is more difficult to manufacture. However no need to further package the reservoir layer. Face reservoir cannot be hermetically sealed and hence proper packaging is required.

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. Metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminum foil)[3].

1.6 *Approaches used in development of Transdermal drug delivery*

a. Membrane permeation controlled systems
b. Adhesive dispersion type systems

c. Matrix diffusion controlled systems
d. Micro reservoir type controlled systems

a) Membrane Permeation Controlled Systems

The release of drug molecules from this type of delivery system is controlled by modulating;

- Partition coefficient.
- Diffusivity of the drug molecule and the rate controlling membrane.
- Thickness of the membrane.

The drug reservoir is totally encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium e.g. silicon fluid. The rate controlling membrane can be micro porous or nonporous polymeric membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface.

Marketed systems

- Transderm-Nitro system for once a day.
- Transderm-Scop system 3days medication.
- Catapres-TTS for weekly treatment.

b) Adhesive Dispersion Type Systems

Two types of patch constructions are offered with the best transdermal performance: Monolithic type that contains active substance dispersed in the adhesive. The release of drug molecules from this type of delivery system is controlled by modulating.

- The permeability of the adhesive polymer
- Thickness of the adhesive layer
- Loading capacity

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied.

e.g: Deponit system and Frandol tape.

c) Matrix Diffusion Controlled Systems

Release is controlled by controlling;

- Loading level
- Polymer solubility of the drug
- Diffusivity in the polymer matrix

The drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then molded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc e.g. nitro-dur.

d) Micro Reservoir Type Controlled Systems

These are considered as combination of reservoir and matrix dispersion type. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shear mechanical force to form unleachable microscopic spheres of drug reservoir.

This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness. Depending upon the physicochemical property of the drug and

the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim e.g. nitrodisc.

- Drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-soluble polymer.
- Dispersing the drug suspension homogenously in a lipophilic polymer. Silicone oil by high energy dispersion techniques.
- Several discrete, unleachable microspheric spheres of drug reservoir are formed.
- Stabilisation by immediate cross linking of polymer chains in-situ. Medicated disc is formed e.g. nitrodisc[5].

1.7 *transdermal film*

Film is an unsupported, typically organic non-fibrous, thin, flexible material of a thickness not exceeding 0.010 inch. A novel process for the preparation of a pharmaceutical preparation in the form of an polyacrylate film for long-term transdermal administration of systemic pharmaceuticals comprising forming a homogeneous solution of an effective amount of a systemically acting pharmaceutical and a freeze-dried latex of a polyacrylate copolymer of methyl and/or ethyl esters of acrylic acid and methacrylic acid formed by emulsion polymerization and having an average molecular weight of about 800,000 in at least one organic solvent, forming a thin layer of the said solution and drying the layer to form a polyacrylate film and the film product produced by the said process[6].

1.8 *transdermal gel*

As the pace of drug discovery accelerates, the route of administration is increasingly being viewed as a critical component of therapeutic business strategies and an integral part of the drug development process. While oral administration remains the dominant method for delivering drugs systemically, a significant number of new therapeutic compounds will require delivery technologies that avoid or mitigate the metabolic processes associated with oral ingestion of medication. The gels form thin and pliable films, which are easily washable with water. They possess prolonged anti-inflammatory and analgesic activities and physicochemical stability with less systemic side effects and gastric irritation.

Use of transdermal gel compounds as an alternative rescue medication for delayed nausea and vomiting compared to oral medications and rectal suppositories. A majority of surveyed patients expressed satisfaction with the transdermal gels. The survey showed the transdermal gels were helpful as a rescue medication for chemotherapy induced delayed nausea and vomiting. Demand for transdermal drug delivery will benefit from several converging market forces. The shifting population demographics in developed societies will drive an increasing demand for palliative treatments associated with an aging patient base. Continuing efforts to control rising healthcare costs in many western countries will place a greater emphasis on home health care and self-administration of drug therapies for chronic conditions such as arthritis and pain management[7]. Transdermal products that are in clinical development in the US are tabulated in Table 1.1.

Table 1.1
Transdermal products that are in clinical development in the US[8]

S. NO.	Compound	Transdermal drug delivery	Technology development stage
1.	Alprostadil	Gel	Preclinical
2.	Dihydrotestosterone	Gel	Phase III
3.	Estradiol	Gel	Phase III
4.	Testosterone	Gel	Preclinical submitted to NDA
5.	Vaccines	Patch	Preclinical
6.	Rotigotine	Patch	Phase III
7.	Parathyroid hormone	Microneedle	Preclinical
8.	Lidocaine	Iontophoresis	Phase III
9.	Diclofenac	Patch	Preclinical

Gels are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly-like by the addition of gelling agents. Gels are defined as semisolid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by a liquid. A transdermal preparation commonly compounded is pluronic lecithin organogel. It consists of a pluronic (poloxamer) F127 gel (usually 20% or 30% concentration) mixed at a ratio of approximately 1.5 with a mixture of equal parts of isopropyl palmitate and lecithin. This gel vehicle aids in rapid penetration of many active drugs through the skin. Among the gelling agents used are synthetic macromolecules, such as carbomer 934; cellulose derivatives, such as carboxymethylcellulose or hydroxypropyl methylcellulose; and natural gums, such as tragacanth. General classification and description of gels are shown below in Table 1.2.

Table 1.2
General classification and description of gels[9]

S. NO.	Class	Description	Examples
1.	Inorganic	Usually two-phase systems	Aluminum hydroxide gel, Bentonite magma
2.	Organic	Usually single-phase systems	Carbopol, Tragacanth
3.	Hydrogels	Organic hydrogels Natural and synthetic gums Inorganic hydrogels	Pectin paste, Tragacanth jelly Methylcellulose, Pluronic Bentonite gel (10-25%)

4.	Organogels	Hydrocarbon type Animal, vegetable fats Soap base greases Hydrophilic organogels	Petrolatum, Lard, cocoa butter Aluminium stearate with heavy mineral oil gel Carbowax bases

1.9 *NSAIDS*

Non-steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects (reducing inflammation). The term "nonsteroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs are sometimes also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs). The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen partly because they are available over-the-counter in many areas.

Mechanism of action

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927-2004), who later received a Nobel Prize for his work. NSAIDs have antipyretic activity and can be used to treat fever. Fever is caused by elevated levels of prostaglandin E2, which alters the firing rate of neurons within the hypothalamus, that control thermoregulation. Antipyretics work by inhibiting the enzyme COX, which causes the general inhibition of prostanoid biosynthesis (PGE2) within the hypothalamus. PGE2 signals to the hypothalamus to increase the body's thermal set point. Ibuprofen has been shown to be more effective as an antipyretic than acetaminophen. Arachidonic acid is the precursor substrate for cyclooxygenase leading to the production of prostaglandins F, D & E.

Classification

NSAIDs can be broadly classified based on their chemical structure;

a) Propionic acid derivatives

- Ibuprofen
- Naproxen
- Fenoprofen
- Ketoprofen
- Flurbiprofen
- Oxaprozin

b) Acetic acid derivatives

- Indomethacin
- Sulindac
- Etodolac
- Diclofenac

c) Enolic acid (Oxicam) derivatives

- Piroxicam
- Meloxicam
- Tenoxicam

- Droxicam
- Lornoxicam
- Isoxicam

d) Fenamic acid derivatives

- Mefenamic acid
- Meclofenamic acid
- Flufenamic acid
- Tolfenamic acid

e) Selective COX-2 inhibitors (Coxibs)

- Celecoxib (FDA alert)
- Rofecoxib (withdrawn from market[10])
- Valdecoxib (withdrawn from market[11])
- Parecoxib FDA withdrawn
- Lumiracoxib TGA cancelled registration
- Etoricoxib FDA withdrawn

Uses

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease. NSAIDs are generally indicated for the symptomatic relief of the following conditions

- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Pyrexia (fever)
- Renal colic
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth

Pharmacokinetics

Most nonsteroidal anti-inflammatory drugs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma volume. Most NSAIDs are metabolised in the liver by oxidation and conjugation to inactive metabolites which are typically excreted in the urine, although some drugs are partially excreted in bile. Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage.Ibuprofen and diclofenac have short half-lives (2–3 hours). Some NSAIDs (typically oxicams) have very long half-lives (e.g. 20–60 hours).

Adverse effects

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents. These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAIDs therapy[10].

2. *Literatuer survey*

Bhalla and Toddwala (1988) concluded that films possessing appropriate physico-chemical qualities were tested for in vitro and in vivo drug diffusion pattern, stability and skin

irritation. The films were found to be free from skin irritation and stable at room temperature but adversely affected by extremes of humidity or high temperature. Both systems gave adequate release of drug and diffusion through skin into systemic circulation when tested on human volunteers[11].

Rao and Diwan (1996) studied that tensile strength of films decreased with increase of PVP fraction in the film. Permeability of films increased with increasing PVP concentration and this may be due to leaching out of PVP fraction, which leads to improved porosity and permeability. Free films composed of CA: PVP (2:1) can be used as rate of controlling membranes for the development of Transdermal Drug Delivery systems (TDDS) systems using a suitable drug reservoir[12].

Rao et al (1997) concluded that water vapor transmission and drug diffusion through the free films followed zero order kinetics and decreased with increasing the film thickness.Diffusion of drugs through the free films of CA was extended over a longer period of time at a controlled rate and thus, these can be used as rate controlling membranes for the development of a transdermal drug delivery system[13].

Hosny et al (1998) concluded that prazosin release from polymeric films containing carboset 525: Eudragit RL 100 in a 1:1 ratio was significantly ($p < 0.05$) higher than from films in a 1:0.25 ratio and non-significantly ($p > 0.05$) higher than from those containing 1:0.5, 1:3 polymer ratios and non-significantly lower from those containing 1:4 polymer ratios. The enhancers were found to increase the W.V.P. and the permeability constant (*P*) and the results were in very good agreement with the effect of enhancers on the in-vitro drug release. The DSC thermograms showed that the enhancers physically interacted with either or both of the polymeric film materials and prazosin which could be one of the reasons for the improvement in the release of the drug from these polymeric films[14].

Rao et al (1998) concluded that the films composed of ethyl cellulose: poly vinyl alcohol: drug (8:2:2) and (8:2:3) exhibited good anti-inflammatory activity over a period of 24h.Prevention of ulcerogenicity of indomethacin was observed by transdermal route compared to oral administration[15].

Murthy et al (2001) concluded that the formulations exhibited good stability at all storage conditions. The substitution of chemical enhancer by magnetic field in transdermal delivery systems appears to be possible[16].

Murthy and Hiremath (2002) studied that the formulation of transdermal drug delivery system for simultaneous delivery of theophylline and salbutamol sulphate is feasible and the system is capable of maintaining the therapeutic levels of the drugs in the blood. The in vivo evaluation proved our assumptions of desorption -release to be practical than just hypothetical[17].

Arora and Mukherjee (2002) concluded that the diclofenac diethylamine can be formulated into the transdermal matrix type patches to sustain its release characteristics and the polymeric composition (PVP/EC, 1:2) was found to be the best choice for manufacturing transdermal patches of diclofenac diethylamine among the formulations studied[18].

Hermes and Narayani (2002) **c**oncluded that the alginate films and beads show good potential for long term systemic delivery of protein / macromolecular agents. The alginate beads will be highly suitable as oral route whereas the films would be used for transdermal route[19].

Khatun et al (2004) concluded that at low drug load, highest amount of drug was released from films containing poly ethylene glycol 1500 (more than 95%). With this formulation, more than 75 % of active principle was released after 8 hours while only 12 % of naproxen was liberated in the first hour of dissolution. Increasing drug load increased the rate and extent of drug release from eudragit RS films; however this effect was minimized when PEG 4000 was used as release modifier. Inclusion of poly ethylene glycol in eudragit RS films caused the drug to be released by diffusion (Fickian) kinetics whereas PVA and hydroxyl propyl methyl cellulose containing formulations released drug by diffusion mechanism coupled with erosion[20].

Mullaicharam et al (2004) studied the drug release across various diffusion barriers that include cellophane membrane and rat abdominal skin. The prepared patches were evaluated for thickness, drug content and stability. The permeation rate from various diffusion barriers was compared. The hydroxyl propyl methyl cellulose films showed a greater rate of release compared to that of CMC across all the barriers used[21].

Murthy and Chowdary (2004) **s**tudied that good linear relationships were observed between wall thickness of microcapsules and drug release rate in each case. Good linear relationships were observed between permeability of ethyl cellulose films and drug released from ethyl cellulose microcapsules[22].

Kulkarni et al (2004) **s**tudied that films produced are transparent, smooth and flexible without plasticization. The time taken for permeation of 50% of drug (T50) through excised rat skin was 120, 62 and 90 min for chitosan, polymer-I and polymer-II respectively[23].

Tanwar (2005) **s**tudied that prepared films exhibited satisfactory physico-chemical characteristics. Incorporating PEG-400 and tween 60 into the films enhanced the permeation across guinea-pig skin; permeation rate was greater with films containing PEG-400.The permeation followed zero order kinetics and mechanism was found to be matrix diffusion[24].

Siemann (2005) **c**oncluded that the oldest technology for the production of thin polymer films is nowadays used for niche products with high quality requirements such as photographical film base, flexible printed circuits, high-temperature resistive films, loudspeaker membranes etc. The future of solvent cast technology will be closely linked to the need of optical films by the emerging liquid crystal. Display industry or other new optical applications which require polymer films with outstanding properties[25].

Nicoli et al (2005) concluded that films are not self-adhesive but become adhesive when applied to wet skin. Permeation experiments were performed from films with different drug loadings using rabbit ear skin as barrier. The permeation profile is not linear, but shows a sort of burst effect in the early times of permeation, probably owing to the presence of solid drug and/or to a certain degree of “conserved supersaturation” in the solid phase[26].

Amnuaikit et al (2005) ***s**tudied* that the moisture uptake capacity and drug release rate increased with the increase of PVP in each preparation. In vitro skin permeation study showed that cineole was the most promising enhancer among the enhancers examined in the present study and suggested that the suitable compositions of film preparation would be EC: PVP: PPL = 6:3:4 with 10% (w/w)

cineole and 7:2:4 with 10% (w/w) PG and cineole, which provided high skin permeation rates at 93.81 ± 11.56 and 54.51 ± 0.52 µg/cm^2/h, respectively[27].

Sheng et al (2006) **s**tudied that the ketoprofen dissolves very rapidly in small intestine, implying that its absorption will be predominantly controlled by gastric emptying, and only minimally limited by the subsequent dissolution processes. This behavior is very similar to BCS I drugs, thus ketoprofen may be considered for possible waivers of bioequivalence[28].

Nicoli et al (2006) **s**tudied that the film was more efficient suggesting that a smaller area or a lower drug loading could be employed. The results obtained show that the bioadhesive film can be a promising and innovative therapeutic system for the transdermal administration of oxybutynin[29].

Das et al (2006) observed that the maximum skin permeability was attained at a loading dose of 10% w/w in the film. The *in vitro* flux decreased gradually at higher concentration up to 13% w/w study has demonstrated the potential of the fabricated pseudo latex transdermal films for sustained release of trazodone hydrochloride. The concentration of triethylcitrate in the film markedly affected the skin permeation properties of trazodone hydrochloride[30].

Kumar and Rani (2006) concluded that to overcome all these drawbacks, liposomes of methotrexate for transdermal drug delivery were formulated and evaluated for drug entrapment, particle size and microscopically[31].

Gattani et al (2006) **c**oncluded that the polymeric matrix-type transdermal films of ondansetron hydrochloride prepared with different grades and ratios of polymers holds potential for transdermal delivery. A slow and controlled release of drug versus time is linear and this constitutes the basis for transdermal delivery of ondansetron hydrochloride[32].

Nanjwade et al (2006) **s**tudied that matrix type of controlled release transdermal system containing isosorbide dinitrate can be satisfactorily established and cellulose acetate can be used as polymer for formulation of thin, uniform, flexible films by the method of casting on mercury surface[33].

Murthy and Kishore (2007) **c**oncluded that the polymers and solvents used in the preparation of films have shown significant influence on the water vapor transmission, drug diffusion and permeability of the films[34].

Murthy and Kishore (2007) **c**oncluded that the solvent evaporation technique gave thin uniform films. Water vapor transmission and drug diffusion rate of films followed zero order kinetics. Drug release was governed by peppas model. Diffusion exponent of release profile (slope) has a value of n>1, which indicates non anomalous transport diffusion[35].

Jain et al (2007) **s**tudied that the application of clindamycin phosphate gel after the pretreatment of skin with adapalene gel for 5 min may contribute significantly to the increased efficacy of therapy[36].

Lakshmi et al (2007) **s**tudied that the human repeated insult patch test did not produce any significant irritation or sensitization on healthy human volunteers. At Week 12, with niosomal methotrexate gel, there was reduction in total score from 6.2378±1.4857 to 2.0023±0.1371. These results suggest that niosomal methotrexate gel is more efficacious than placebo and marketed methotrexate gel[37].

Siddique et al (2007) **s**tudied that hydroxy propyl methyl cellulose is very versatile release agent. Although it is itself hydrophilic it has been used as a drug release retardant for several drugs and is useful in case of highly water soluble drug also. Thus hydroxy propyl methyl cellulose has been proved that it works well with soluble and insoluble drugs and at high and low dosage levels[38].

Swamy et al (2008) **s**tudied that with increase in plasticizer content, there was a decrease in breaking force of films, whereas, there was an increase in mean thickness and piercing load in both the cases[39].

Murthy and Kishore (2008) **c**oncluded that all gels were found to exhibit plastic flow. The gel formulations showed good extrudability, spreadability and viscosity. Formulation G_6 was found to have better permeation and hence may be considered as candidate for development of topical dosage forms[40].

Murthy et al (2008) **c**oncluded that cellulose acetate films of hydroxyl propyl methyl cellulose, poly ethylene glycol 4000,poly vinyl pyrrolidone, sodium CMC are permeable to drug and drug diffusion was extended over a long period of time at a controlled rate, hence these can be used as rate-controlling membranes for fabrication of transdemal systems[41].

Omray et al (2008) studied the mesophasic micro reservoir comprises lyotrophic liquid crystals. The liquid crystals were prepared of Brij-35, cetosteryl alcohol and propranolol and evaluated for parameters viz. anisotropy, size and size distribution and drug entrapment efficiency. The system was also studied for tensile strength, moisture content, water vapor transmission, drug content, anisotropy and In vitro drug release studies[42].

Gupta et al (2008) were prepared transdermal drug delivery system of tizanidine hydrochloride by using different combinations of a hydrophobic polymer, ethyl cellulose and two hydrophilic polymers namely poly vinyl pyrrolidone and poly vinyl alcohol were prepared by solvent evaporation method. The patches containing lipophilic polymer containing and lipophilic-hydrophilic polymer combinations exhibited slow release in comparison to patches containing hydrophilic polymers. Drug release data of selected patch (T_8) showed good fit into Higuchi equation[43].

Shinde et al (2008) observed that the significant improvement of the release observed in formulations containing triethyl citrate. Formulation F14 containing triethyl citrate had highest tensile strength as well as folding endurance. From the drug release profile it is concluded that the concentration of the Eudragit increases in the formulation with increase in the release of drug from the patch[44].

Ammar et al (2008) studied the chitosan has film forming ability, bioadhesive and absorption enhancing properties. The above-mentioned results shed light on feasibility of utilizing chitosan as an effective, safe transdermal delivery system for glimepiride characterized by increased patient compliance and better and better control of the disease[45].

Wahid et al (2008) concluded that diffusion is dominant mechanism for drug release following non-fickian type of diffusion. Among all the prepared films, D_3 was better formulation based on the in-vitro skin permeation studies as it sustained the release of drug for longer duration with out significantly releasing the drug in a burst manner in the initial hours. Etoricoxib transdermal patches could be successfully prepared using chitosan, modified chitosan and chitosan –HPMC blend[46].

Gattani et al (2008) **c**oncluded that the polymeric matrix type transdermal films of lovastatin prepared with different grades and ratios of polymers holds potential for transdermal delivery. A slow and controlled release of drug release of drug release versus time is linear these supporting the test products for transdermal films[47].

Bhatt et al (2008) **c**oncluded that for potential therapeutic use, monolithic drug matrix films MF-3, composed of EC: PVP (3:2), may be suitable for the development of a transdermal drug delivery system of metoprolol tartrate[48].

Desai *et al* (2008) concluded that citral and dimethyl formamide as permeation enhancer showed the best permeability as compared to sodium tauroglycholate, sodium lauryl sulfate etc[49].

Nappinnai et al (2008) **c**oncluded that the F_3 (HPMC content 2% w/w) shows the maximum release of the drug when compared to the marketed product. F_3 is pharmaceutically stable and effective formulation as proved by in-vitro and in-vivo study[50].

Kulkarni and Nagarsenkar (2008) **c**oncluded that BMs of rofecoxib and BCD exhibited improvement in apparent aqueous solubility and in vitro dissolution profile of the drug owing to partial amorphization of drug as revealed by DSC and XRD studies[51].

Sanap et al (2008) **c**oncluded that the thin, flexible, smooth and transparent films were obtained with HPMC and EC polymers using glycerine and dibutyl phthalate as plasticizers. Thickness, weight and drug contents of all the formulations remained uniform with low SD values. The monolithic systems were found to be stable at 37°C and 45°C. SEM studies confirmed that there was uniform distribution of drug in the selected film. Studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation[52].

Patel et al (2009) concluded that furosemide transdermal films using Ec/Hpmc polymer blend were prepared. Among the penetration enhancers, propylene glycol, dimethyl sulfoxide, and isopropyl myristate used the highest permeation rates were noticed with propylene glycol. Incorporation of HPMC enhanced the flux of the drug and also was responsible for the swelling coupled diffusion controlled drug release[53].

Jadhav et al (2009) concluded that the polymeric matrix-type transdermal films of DS prepared with different grades and ratios of polymers holds potential for transdermal delivery. Developed formulation has the best effective combination of polymer but slight modification required to achieve therapeutic plasma concentration[54].

Chandra et al (2009) studied that microemulsions increased the permeation rate of dexamethasone compared with the control. The optimum formulation consisting of 0.1% dexamethasone, 10% olive oil, 70% egg lecithin:IPA (2:1), and water showed a permeation rate of 54.9 µg/cm ^{2} /h. The nutmeg oil-based transdermal microemulsion gel system demonstrated 73.6% inhibition in rat paw edema. Thus, microemulsion-based transdermal systems are a promising formulation for dermal delivery of dexamethasone[55].

Patil et al (2009) concluded that, stem gum of Moringa oleifera has enormous potential for use in the preparation of polymeric films as drug delivery systems. The various in vitro tests have been performed. In vivo studies

were conducted in rats and results showed significant wound healing activity property[56].

Chandra et al (2009) **s**tudied that the reservoir type transdermal patch for the delivery of ketorolac appeared to be feasible for delivering ketorolac across the skin. The increase in the concentration of eucalyptus oil enhanced the drug permeation[57].

Pattnaik et al (2009) studied that the therapeutic system was found to be dermatologically non-irritant and hence, a therapeutically effective amount of alfuzosin hydrochloride can be delivered via a transdermal route[58].

Patel et al (2009) concluded that the release pattern follows zero order kinetics, which fits, into Peppa's model, indicating that mechanism of drug release by swelling. The optimized formulation containing Carbopol 934: Eudragit L100 (3:7), with enhancer hyaluronidase showed 84% drug release after 24 hours[59].

Pandit et al (2009) concluded that the tolterodine tartarate holds good promise for administration via transdermal route for the treatment of overactive bladder. The possibility to formulate tolterodine tartarate as a transdermal film and the various parameters that were evaluated helps to understand the usefulness of tolterodine tartarate as a delivery system of tolterodine. Tolterodine tartarate in the form of transdermal films can be used as a drug delivery
system for treating overactive bladder for long term therapy[60].

Singh et al (2009) **c**oncluded that the incorporating ketoprofen into bioadhesive gels containing a penetration enhancer in various concentrations enhanced the drug permeation through rat skin and in-vivo performance. Bioadhesive gels of ketoprofen containing oleic acid may offer promise as an anti-inflammatory dosage form, ensuring more effective therapy, but additional experiments should be performed before the formulation is used in humans[61].

Dhamankar et al (2009) concluded that the two novel o/w microemulsions containing ketoprofen were designed for improving transdermal absorption. When microemulsions were gelled, they found to have uniform viscosity, spreadability, elegant appearance and did not produce skin irritation. Drug content at top, middle and bottom of the formulations revealed the percentage of drug close to 100%. The results of physicochemical characteristics are satisfactorily. Both the formulations are superior to marketed formulation in the respect of drug permeation across the membrane[62].

Mittal et al (2009) concluded that the nitrendipine polymeric films containing Plasdone S 630 were found to have higher flexibility compared to those containing PVP K 30. The release of the drug was sustained and it extended over a period of 48 h in all developed films. The IR and TLC studies revealed that there was no interaction between the drug and the polymers used for making matrices. The above data thus support the assumption that these films might be suitable for transdermal application[63].

Ahmed et al (2009) c*oncluded* that the drug(s) were found to release at a constant rate, so Chitosan may be a useful matrix for sustained release of drugs, and cross-linking of the polymer is essential for the management of adult periodontitis. The advantage of Chitosan is that it has a wound healing property, which is a positive effect in anti-bacterial therapy[64].

Shivhare et al (2009) concluded that log P value of drug indicate that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch. The DSC, IR and TLC results suggest that the drug and polymers are compatible with each other. Formulation A5 has showed maximum release and highest zero order rate constant i.e. (k Value= 11.8113) and followed Peppas model and mechanism of release was Fickian mediated. Hence, the formulation A5 comprising of ERL, ERS, EC and HPMC in the ratio of 6.5:1.25:1.25:1.25 ratios fulfill the requirement of good TDDS[65].

Patel et al (2009) studied prepared formulation with hydrophilic polymer containing permeation enhancer showed best in vitro skin permeation through rat skin as compared with all other formulations. This formulation demonstrated good anti-inflammatory activity against carrageenan-induced edema in wistar albino rats similar to standard formulation[66].

Kannaiyan et al (2009) studied the formulated liopsomal gel having CP of 1.5% concentration would be stable and keeps the medicament for a longer time period from the leaching process of the lipid bilayer. Thus, highly degradable, potent drug can be formulated in this CP gel liposomal drug delivery thus enhancing the potency of the drug and protecting the drug's therapeutic efficacy till the desired period[67].

Purohit et al studied the drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. This experimentation is one of the first few attempts to utilize ayurvedic drugs through TDDS[68].

Garala et al (2009) studied the Medicated monolithic matrix transdermal systems can be prepared from blends of HPMC and ES showed good mechanical performance. Moreover, a general conclusion that can be drawn is that selection of a particular blend formulation can vary the diffusion of the drug significantly. HPMC/ES polymer blends could have potential to formulate TDDS as they have good film forming property and mechanical strength[69].

3. *Summary & conclusion*

This review shows that new and alternative drug delivery systems are currently the focus of many research activities. Efficacy, safety, convenience of use is important factors that need to be considered when developing alternate drug delivery systems. Research related to the development of NDDS is now a day is highly preferred and facilitating field of pharmaceutical world. It has crossed the infancy period and now touching the height of growth from the pharmacy point of view. The transdermal drug delivery is one of the promising route of drug delivery system, since it by passes the first pass metabolism, avoids inactivation of drugs by pH effects and enzymes present in GI tract, provides a continuous mode of administration at rates approaching zero order similar to that provided by an intravenous infusion, increase the half life of the drug, the delivery is non-invasive, no hospitalization is required, and improves patient compliance.

There are more than million of peoples across the world who suffers from various arthritic disorders like rheumatoid arthritis, osteoarthritis or other related conditions. The side effects of NSAIDs take through the oral route, especially their propensity to cause gastritis or ulcers, often impede their long-term use. Transdermal drug delivery system with its unique profile addresses this problem. System can be effectively used to treat pain and inflammation associated with musculoskeletal disorders and soft tissue injury. NDDS has really revolutionized pain management. It uses

the skin, the most readily accessible organ of the human body, and provides largest area of administration to deliver the needed medication. The NDDS innovation is especially relevant to those who are sensitive to drug toxicity and it helps avoid gastrointestinal disorders. NDDS application of NSAIDs would minimize the amount of drug that circulates in the blood and concentrates the drug locally at the site of pain. It produces minimal drug level in the blood serum, with likelihood of toxicity. This is a significant advantage for patient who needs medication several times a day. NDDS is most suitable to the patient who suffers from chronic arthritic condition those results in inflammation and pain. As this condition predominantly affects the older generation, transdermal delivery is especially convenient, as many old people do not like to or unable to swallow oral medication. This article suggest that administration of NSAIDs by novel drug delivery system at a site of tissue injury delays the onset and lowers the intensity of pain at lower doses than usually administered orally.

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