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Novel Formulation Approaches for Dermal and Transdermal Delivery of Non-Steroidal Anti-Inflammatory Drugs

Alper Okyar[1], Yıldız Özsoy[2] and Sevgi Güngör[2]
[1]*Istanbul University Faculty of Pharmacy Department of Pharmacology, Beyazıt- Istanbul*
[2]*Istanbul University Faculty of Pharmacy Department of Pharmaceutical Technology, Beyazıt- Istanbul, Turkey*

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drug groups. These drugs are used dermally or systemically in treatment of various rheumatic diseases, including rheumatoid arthritis (RA), as well as for osteoarthritis, low back pain and some joint diseases. The mechanism of action of NSAIDs is reversible inhibition of the cyclooxygenase enzyme (COX) and decreasing the synthesis of prostaglandins (Lionberger 2010; Massey 2010). However, these drugs lead to unfavorable effects specifically on the stomach as a result of inhibition of prostaglandins (PGs), which play a role in protection of the gastric mucosa, in systemic administration. The severity of these unfavorable side effects may range from a simple ailment like dyspepsia to peptic ulcer and gastrointestinal hemorrhage. Furthermore, the acidic character of NSAIDs may lead to local irritation and lesions on the gastrointestinal mucosa. Therefore, some NSAIDs are administered percutaneously and transdermally to achieve local or systemic effect as an alternative to oral and parenteral administration (Heyneman et al., 2000; Hooper et al., 2004). In dermal administration, the drug substances have to pass the *stratum corneum (SC)* layer to reach lower layers of the skin and/or to enter systemic circulation. In this context, formulation of the product may play a key role for penetration and absorption of the active ingredient (Lee & Maibach, 2006). Several formulation approaches for cutaneous administration of NSAIDs have been employed. The conventional pharmaceutical forms particularly used for dermal administration to achieve local effect are gels, creams and ointments (Williams, 2003). Furthermore, studies on novel drug delivery systems are available for transdermal administration of NSAIDs. These new approaches include liquid crystals, nano/micro emulsions, liposomes, solid lipid particles and patches. These systems are used to enhance cutaneous passage of drugs into systemic circulation and to target different layers of the skin (Guy, 2010; Santos et al., 2008; El Maghraby et al., 2008; Ceve, 2004). Different approaches have been performed to enhance cutaneous passage of drugs with the objective of overcoming the low skin permeability (Guy, 2010; Tromer & Neubert,

2006). The most frequently used approach is to include penetration enhancers in formulations. In addition to penetration enhancers, there are studies available in which physical methods such as iontophoresis is used in improving of skin delivery of drugs (Guy, 1996; Benson, 2005; Williams, 2003).
The chapter deals with the classification and mechanisms of action of NSAIDs used in treatment of various rheumatic diseases as well as for osteoarthritis, low back pain and some joint diseases. The advantages of skin delivery of NSAIDs to target affected tissues and/or to achieve systemic effect are also emphasized. In particular, recent studies in which novel drug delivery systems were developed for dermal and transdermal administration of NSAIDs are summarized.

2. Non-steroidal anti-inflammatory drugs (NSAIDs)

2.1 General view and classification of NSAIDs

NSAIDs are used for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis, posttraumatic conditions (e.g. distortion, contusion), for relieving mild to moderate pain of varied origin, reducing fever, as well as for preventing local inflammation such as gout (Hinz & Brune, 2008; Lionberger et al., 2011; Patrono & Rocca, 2009). NSAIDs are employed in systemic as well as local dosage forms particularly for musculoskeletal pain and patients with inflammatory joint disorders. NSAIDs possess antipyretic effect in addition to analgesic-anti-inflammatory actions. NSAIDs may be responsible for side effects such as acute renal failure, undesirable central nervous effects, e.g. dizziness, allergic reactions and fluid retention in the body. Beside some side effects of NSAIDs mentioned before, NSAIDs lead to unfavorable effects on the stomach as a result of inhibition of prostaglandins, which play a role in protection of the gastric mucosa, in systemic administration e.g. oral, parenteral. The severity of this unfavorable gastrointestinal side effect may range from a simple ailment like dyspepsia to gastric bleeding potentially resulting in admission to hospital, necessitating surgery or even resulting in death (Hooper et al., 2004). Furthermore, the acidic character of NSAIDs may lead to local irritation, and lesions on the gastrointestinal mucosa are known as NSAIDs gastropathy (Heynemann et al., 2000). Within the past 20 years many COX inhibitors were removed for undesired drug effects shortly after entering the market e.g. benoxaprofen and isoxicam (Brune et al., 2010). Therefore, some NSAIDs are administered percutaneously to achieve local or systemic effect as an alternative to oral and parenteral administration (Heyneman et al., 2000; Hooper et al., 2004). NSAIDs are classified by their chemical structures as shown in Table 1.

2.2 Mechanism of anti-inflammatory effect of NSAIDs

NSAIDs usually act through decreasing reactions of inflammation that is accompanied with pain. It is known that prostaglandin (PG) derivatives, that are formed from arachidonic acid through COX enzyme, play an important role in formation of inflammation, and that the PGE_1 and PGE_2 levels are increased in the synovial fluid in patients with rheumatoid arthritis. All NSAIDs inhibit the COX enzyme and act through decreasing the synthesis of PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A2 (TxA_2) and prostacycline (Lionberger et al., 2010; Massey et al., 2010). Two isoforms of COX (COX-1 and COX-2) were identified and

Salicylates	**Para-aminophenol derivatives**	**Pyrazolone derivatives**	**Phenylpropionic acid derivatives**	**Phenylacetic acid derivatives**	**Indoleacetic acid derivatives**	**Fenamic acid derivatives**	**Oxicams**	**Other drugs**	**COX-2 selective NSAIDs**
Acetylsalicylic acid	Acetaminophen	Aminopyrine	Ibuprofen	Diclofenac	Indomethacin	Mefenamic acid	Piroxicam	Proquazone	Etodolac
Diflunisal		Metamizole	Ketoprofen	Nabumeton	Acemetasin	Flufenamic acid	Tenoxicam	Azapropazone	Meloxicam
Sodium salicylate		Phenylbutazone	Phenoprofen	Fenclofenac	Tolmetin	Etofenamate	Lornoxicam	Methotrimeprazine	Nimesulide
Salicylic acid		Oxyphenbutazone	Flurbiprofen	Alclofenac	Ketorolac	Tolfenamic acid	Isoxicam	Benzydamine	Selecoxib
Salicylamide		Propyphenazone	Indoprofen	Felbinac	Sulindac	Meclofenamate		Nabumetone	Rofecoxib
		Amidopyrine	Naproxen	Bufexamac		Niflumic acid		Etofenamate	Etoricoxib
			Fenbufen	Aceclofenac					Lumiracoxib
			Zomepirac						Parecoxib
			Dexibuprofen						Valdecoxib
			Dexketoprofen						
			Oxaprozin						
			Tiaprofenic acid						
			Suprofen						

Table 1. Classification of NSAIDs according to chemical structure (Heynemann et al., 2000; Hadgraft et al., 2000; Marnett, 2009).

studies of their regulation and sites of expression led to the hypothesis that it is the molecular target for the anti-inflammatory and analgesic effects of NSAIDs. COX-1 is important for production of gastric mucus and maintenance of renal blood flow. On the other hand, COX-2 is induced by several cytokines, growing factors and endotoxins and plays a role in the inflammatory process observed at the site of inflammation. Nonselective NSAIDs inhibit both COX-1 and COX-2, and the current hypothesis is that COX-2 inhibition is responsible for the anti-inflammatory effects of NSAIDs, whereas COX-1 inhibition is responsible for some other undesired side effects, in particular for gastrointestinal toxicity. Therefore selective inhibition of COX-2 may prevent undesirable gastrointestinal effects of NSAIDs. The discovery and clinical development of selective COX-2 inhibitors (COXIBs) were achieved in the early 1990s. COXIBs have anti-inflammatory effects without side effects on the stomach as compared to traditional NSAIDs. However, these new NSAIDs also possess some side effects, since inhibition of COX-2 affects kidney function and blood pressure and possibly other physiological parameters (Brune & Hinz, 2004; Marnett, 2009; Patrono & Rocco, 2009; Mitchell et al., 1994). Rofecoxib and valdecoxib was withdrawn from the market due to serious cardiovascular side effects, and lumiracoxib was removed from several markets for serious liver toxicity unrelated to COX-2 inhibition. Celecoxib has been marketed in the United States, and celecoxib and etoricoxib was marketed in Europe (Hinz & Brune, 2008).

2.3 Physicochemical properties of NSAIDs

Table 2 demonstrates the open chemical formulas and physicochemical properties of NSAIDs, which have dermal and transdermal commercial preparations and of the molecules which are potential candidates in this group.

The physiochemical properties of drugs are important in dermal and transdermal administration (Potts and Francoeur, 1991; Kalia et al., 1998; Prausnitz & Langer, 2008). The ideal candidate drugs have the following properties: water-solubility (> 1 mg/ml), lipophilicity (log P= 1-3), low molecular weight (< 500 Dalton) and low melting temperature (< 200°C) (Guy, 2007). As can be seen in Table 2, all drugs are under 400 Dalton. The Log P values, which indicate lipophilic characteristics of pharmaceuticals, vary between 2.0 and 3.8 except for flurbiprofen, etofenamate and lumiracoxib. In other words, they have medium lipophilicity. Other NSAIDs except meloxicam and tenoxicam have a melting point under <200°C. Due to these physicochemical properties, NSAIDs are ideal molecules for dermal administration. As a matter of fact, dermal/transdermal commercial preparations of most of NSAIDs are available in pharmacies. Studies on development of skin delivery systems of other molecules are in progress.

3. Dermal and transdermal administration of NSAIDs

3.1 Skin transport

Human skin is the largest organ in our body with its size about 1.8-2.0 m^2. It is a well-engineered organ that protects organism against environmental factors and regulates heat and water loss from the body. It is also easily accessible due to its large surface area. Therefore, it offers an ideal application site to deliver therapeutic agents for both local and systemic actions. The skin consists of three main layers; the epidermis, the dermis, and the

hypodermis. In particular, *stratum corneum* (SC), the outermost layer of epidermis is formed by dead and keratinized cells, and thus it is a unique barrier to passage of drugs through the skin (Williams, 2003).The drug substances from dermal or transdermal formulations have to pass through the SC layer to reach lower layers of the skin and/or to enter systemic circulation. The physicochemical characteristics of drug molecules and the types of the formulations are an effective factor in both dermal and transdermal delivery (Hadgraft, 1999). The drugs pass through the skin via three different routes, which are transcellular, intercellular and/or transappendageal (shunt) routes (sweat glands, hair follicles, sebaceous glands) (Williams, 2003).

3.2 The superiorities and limitations of dermal and transdermal delivery

There are two pharmacological approaches in dermal administration of drugs, which are dermal and transdermal. In dermal administration, the applied formulation ensures localization of drugs in dermal layers. In transdermal administration, the drugs reach the dermis of skin via carrier systems and then go into systemic circulation (Williams, 2003).
In dermal administration, the access of drugs to systemic circulation is prevented or minimized. Therefore, the systemic adverse effects of drugs are avoided. The advantages of transdermal administration include high patient compatibility with treatment, ability to discontinue treatment any time necessary, delivery of drug to organism at a controlled rate, ensuring fixed plasma drug level and eliminating the hepatic first-pass effect (Guy, 1996).
NSAIDs administered dermally and transdermally penetrate slowly and in small quantities into the systemic circulation. These approaches also prevent high local drug levels in the alimentary tract and direct toxicity of NSAIDs e.g. vomiting, dyspepsia. Systemic administration of NSAIDs may cause drug-drug interactions. NSAIDs cause fluid retention in the body and may decrease efficacy of antihypertensive agents. Furthermore, dermal and transdermal formulations have better patient compliance (non-invasiveness) and they can be self-administered (Guy, 1996; Taner & Marks, 2008; Heynemann et al., 2000). It was reported that the use of dermal NSAIDs may have led to a reduction in the total daily dosage of systemic NSAIDs. This would cause an increment in side effects of NSAIDs in long term treatment (Sift Carter et al., 1997). Finally, dermally applied NSAIDs have a superior safety profile to oral formulations. Adverse effects secondary to dermal NSAID application occur in approximately 10 to 15% of patients and are primarily cutaneous in nature (rash and pruritus at the site of application (Heynemann et al., 2000)). NSAI drug concentration should reach therapeutic level in the synovial tissue, synovial fluid and intra-articular tissues during dermal application of NSAIDs. There are a number of factors that influence skin absorption of drugs. The greatest challenge for dermal penetration is SC, the uppermost layer of the skin, which as mentioned previously is the rate limiting step for epidermal drug transport. Therefore several formulation approaches are developed to improve its impermeability characteristics.

3.3 Overcoming the barrier properties of the skin

Several chemical and physical approaches are used to overcome the barrier property of the skin in dermal and transdermal administration of drugs. The most frequently used approach is to include chemical penetration enhancers in formulations. Recently, physical

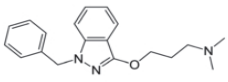
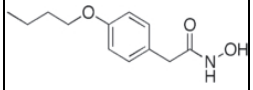
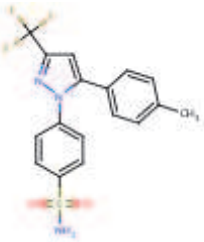
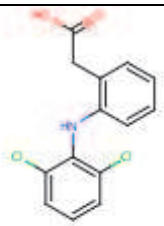
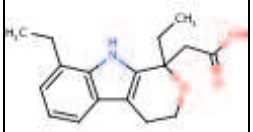
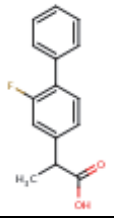
Substance	Chemical Formula	Molecular Weight (g/mol)	Predicted Log P	Melting Point	Predicted aqueous solubility (µg/ml)	pKa	References
Benzydamine		309,4	3.71	160° (bp)	-	9,27	Avdeef et al., 1998. Quane et al.,1998
Bufexamac		223,3	2,43	154°C	110 µg/ml	9,24	Hadgraft et al., 2000
Celecoxib		381,4	3,5	157-158°C	3,3 µg/ml	11.1	http://www.drugbank.ca
Diclofenac		296,1	3,28	157°C	12 µg/ml	4,18	Hadgraft et al., 2000
Etodolac		287,4	2,5	145°C	16 µg/ml	4,65	http://www.drugbank.ca
Flurbiprofen		224,3	4,12	110,5°C	2,7 µg/ml	4,14	Hadgraft et al., 2000

Table 2. Chemical formulas and physicochemical properties of NSAIDs.

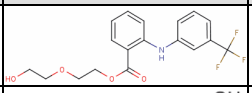
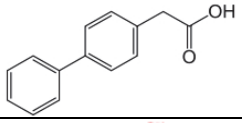
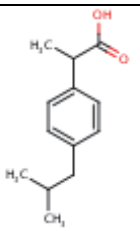
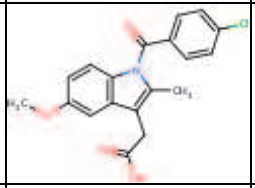
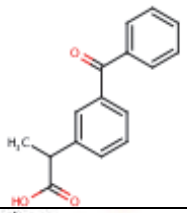
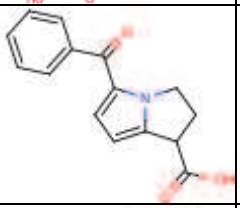
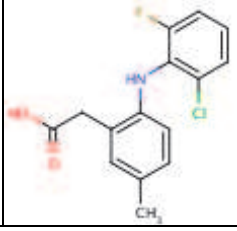
Substance	Chemical Formula	Molecular Weight (g/mol)	Predicted Log P	Melting Point	Predicted aqueous solubility (µg/ml)	pKa	References
Etofenamate		369,3	4.99	130–135°C (bp)	Practically insoluble in water	-	http://www.chembase.com
Felbinac		212,2	3,26	164°C	8 µg/ml	4.3	Pygall et al., 2009
Ibuprofen		206,3	3,72	76°C	14 µg/ml	4,41	Hadgraft et al., 2000
Indomethacin		357,8	3,10	155°C	25 µg/ml	4,18	Hadgraft et al., 2000
Ketoprofen		254,3	2,81	94°C	150 µg/ml	4,23	Hadgraft et al., 2000
Ketorolac		255,3	2,1	165-167°C (trometh amine salt)	25 mg/mL (trometha mine salt)	3,5	http://www.drugbank.ca
Lumiracoxib		293,7	4,56	139-141°C	5,49 µg/ml	15,87	http://www.drugbank.ca

Table 2. Continued.

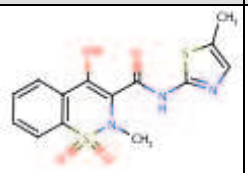
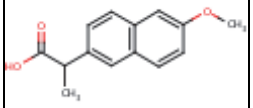
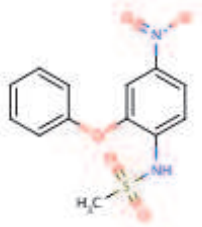
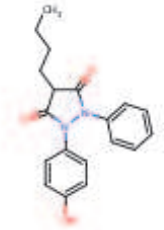
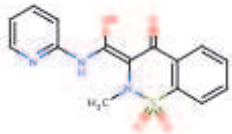
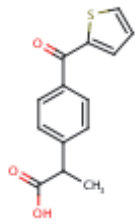
Substance	Chemical Formula	Molecular Weight (g/mol)	Predicted Log P	Melting Point	Predicted aqueous solubility (µg/ml)	pKa	References
Meloxicam		351,4	1,9	242 - 250°C	7,15 µg/ml	4,08	http:// www.drug bank.ca
Naproxen		230,3	3,00	155,3°C	23 µg/ml	4,4	Hadgraft et al., 2000
Nimesulide		308,3	2,56 1,79	143-144°C	18,2 µg/ml	6,46	http:// www.drug bank.ca
Oxyphen-butazone		324,4	2,79 3,83	96°C	256 µg/ml	9,29	http:// www.drug bank.ca
Piroxicam		331,4	1,46	199°C	870 µg/ml	13,92	Hadgraft et al., 2000
Suprofen		260,3	3,16 3,53	124,3°C	42,2 µg/ml	3,91	http:// www.drug bank.ca

Table 2. Continued.

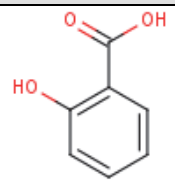
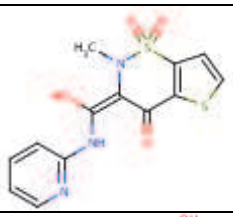
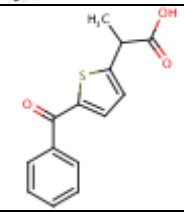
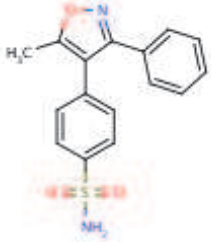
Substance	Chemical Formula	Molecular Weight (g/mol)	Predicted Log P	Melting Point	Predicted aqueous solubility (µg/ml)	pKa	References
Salicylic acid		138,1	2,4	158°C	2,24 g/mL	2,97	http:// www.drug bank.ca
Tenoxicam		337,4	1,82 1,22	211°C	277 µg/ml	13,63	http:// www.drug bank.ca
Tiaprofenic acid		260,3	2,42	96°C	450 µg/ml	4,05	Hadgraft et al., 2000
Valdecoxib		314,4	3,32 2,82	162-164°C	34,8 µg/ml	9,4	http:// www.drug bank.ca

Table 2. Continued.

methods such as iontophoresis that enhance penetration of drug molecules through the skin are applied (Mitragotri et al., 2000; Tao & Desai, 2003). Furthermore, vesicular carriers, microemulsions, lipidic and polymeric particulate carrier systems ensure dermal administration of drugs by dermal targeting and enterance of drugs into systemic circulation (Neubert, 2011; Benson, 2005).

3.3.1 Chemical enhancers

Chemical penetration enhancers reversibly change the structure of the skin to improve the flux of drugs through the skin. The mechanism of action of penetration enhancers is explained by Lipid-Protein-Partition (LPP) Theory (Williams & Barry, 1991). According to this theory, penetration enhancers i) disrupt the lipid structure in intercellular domain of SC, or ii) denature or change the conformation of keratin in the intracellular domain and/or iii) improve drug partition to SC and thus establish a drug reservoir in SC to act (Williams &

NSAIDs	Enhancers	Results	Refs
Diclofenac	Oleic acid(OA)/ d-limonene	Addition of the mixture of oleic acid/d-limonene as enhancer into diclofenac sodium formulations has been found to be effective for the dermal and subdermal injuries.	Escribano et al., 2003
Diclofenac	Dimethyl sulfoxide (DMSO)	Dermal administration of diclofenac containing DMSO vehicle has been found to be effective for knee osteoarthritis, and has showed better tolerability than oral diclefenac.	Simon et al., 2009
Etodolac	terpenes	Gel containing anethol increased absorption of etodolac (1,5-fold) significantly in excised rat skin, as compared to control gel.	Taş et al., 2007
Flurbiprofen (nitro ester)	Transcutol®/(OA) lauroglycol isopropyl myristate (IPM)	The efficacy and safety of dermal nitro ester of flurbiprofen was shown with lipophilic ointment containing chemical enhancers.	Minghetti et al., 2003
Flurbiprofen	Turpentine oil	The bioavailability of transdermal patch formulation flurbiprofen containing turpentine oil has been shown to increase 5.56 times with respect to its oral administration.	Charoo et al., 2008
Flurbiprofen	l-menthol/ethanol	Flurbiprofen gel containing ethanol (25%) and l-menthol (3%) has showed high in vivo absorption rate in rabbits.	Morimoto et al., 2000
Flurbiprofen	Linoleic acid (LA)/ /linolenic acid (LNA)/(OA) Palmitic acid (PA)	Fatty acids (PA, OA, LA, and LNA) extracted from Botryococcus braunii was found effective enhancers to improve the skin delivery flurbiprofen.	Fang et al., 2004
Ibuprofen	Ethanol	The flux of ibuprofen was increased by the ethanol (>10-fold flux enhacement) across silicone membrane and human skin.	Watkinson et al., 2009
Ibuprofen	Propylene glycol (PG)	PG and (PG: water) systems has increased the fluxes of ibuprofen due the increase in skin partition of ibuprofen.	Watkinson et al., 2008
Ketorolac	DMSO/d-limonene eucalyptus oil/ Transcutol®	Eucalyptus oil has showed the highest permeation enhancer effect for the transdermal delivery of ketorolac across rat skin.	Amrish & Kumar, 2009
Ketorolac trometamol	IPM/ Brij 92	Dermal formulations of ketorolac trometamol containing Brij 92 exhibited less gastric side effect and higher anti-inflammatory effect than that of containing IPM.	El-Setouhy & El-Ashmony, 2009
Lumiracoxib	OA	Oleic acid (10%) has increased the flux of lumiracoxib through skin and its retention in viable epidermis.	Moreira et al., 2010

NSAIDs	Enhancers	Results	Refs
Meloxicam	N-methyl pyrrolidone (NMP)	Meloxicam gel containing NMP as a solubilizer exhibited significant higher anti-inflammatory in rats compared to commercial gel formulation.	Bachhav & Patravale, 2010
Nimesulide	OA/ Transcutol®	Oleic acid (3%) in the presence of Transcutol® (30%) has led to a significant increase in permeation of drug across the skin.	Gungor & Bergisadi, 2004
Piroxicam	Lauric acid /OA/LA/LNA	All enhancers showed similar extent of permeation, which was 3-fold higher than that of without enhancer administration.	Santoyo & Ygartua, 2000
Tenoxicam	OA/LA/oleyl alcohol	The highest tenoxicam flux was obtained by the addition of fatty acids at 3% concentration to PG.	Gwak & Chun, 2002
Tiaprofenic acid	terpenes	Gel containing d-limonene increased absorption of tiaprofenic acid (6-fold) significantly in excised pig skin, as compared to control gel.	Okyar et al., 2008
Tiaprofenic acid	terpenes	Gel containing d-limonene increased absorption of tiaprofenic acid (6-fold) significantly in excised rat skin. Gel with d-limonene increased tiaprofenic acid skin absorption of 10-fold in vivo in rats, as compared to control gel.	Okyar et al., 2010

Table 3. Effect of chemical penetration enhancers to increase skin permeation of NSAIDs.

Barry, 2004; Thong HY et al., 2007). Co-solvents such as alcohols, oil alcohols, propylene glycol, diethyleneglycol monoethylether (Transcutol®), and compounds like fatty acids terpenes, Azone®, dimethylsulfoxide (DMSO), pyrrolidones, urea and surfactants are frequently included in dermal/transdermal formulations as penetration enhancers (Williams & Barry, 2004; Mohammed et al., 2007). Table 3 summarizes the penetration enhancers to improve passage of NSAIDs through the skin and the results obtained.

3.3.2 Physical enhancement

Iontophoresis is one of the most frequently used physical methods in improving dermal penetration of drugs. Iontophoresis enhances dermal penetration of drug molecules by applying low levels of electrical currents (0,5 mA/cm^2) (Marro et al., 2002). Unlike passive diffusion-based transdermal administration, particularly, iontophoresis ensures dermal penetration of polar and charged drug molecules in high amounts loaded (Kalia et al., 1998; Sieg & Wascotte, 2009).

There are studies investigating whether the iontophoresis technique enhanced dermal penetration of NSAIDs. Curdy et al. (2001) dermally administered a commercial gel formulation containing piroxicam, and studied dermal penetration of piroxicam by using

both passive and iontophoresis method. They found that application of low electric current enhanced uptake of piroxicam to SC layer. Moreover, a high piroxicam concentration was obtained in the SC, live epidermis and dermis with the iontophoresis application. Mathy and coworkers studied the percutaneous penetration of flurbiprofen on hairless rats (Mathy et al., 2005). They investigated the flurbiprofen concentrations in the dermal and subcutaneous tissue following administration of iontophoresis. The data obtained demonstrated that application of iontophoresis ensured delivery of flurbiprofen at a high input rate to the dermis and underlying tissues at significant amounts, while maintaining low plasma exposure.

4. Conventional formulations and novel approaches in dermal and transdermal delivery of NSAIDs

Conventional dosage forms of NSAIDs which are commercially available and and possible novel carrier systems of NSAIDs to improve their dermal and transdermal delivery are summarized in Fig.

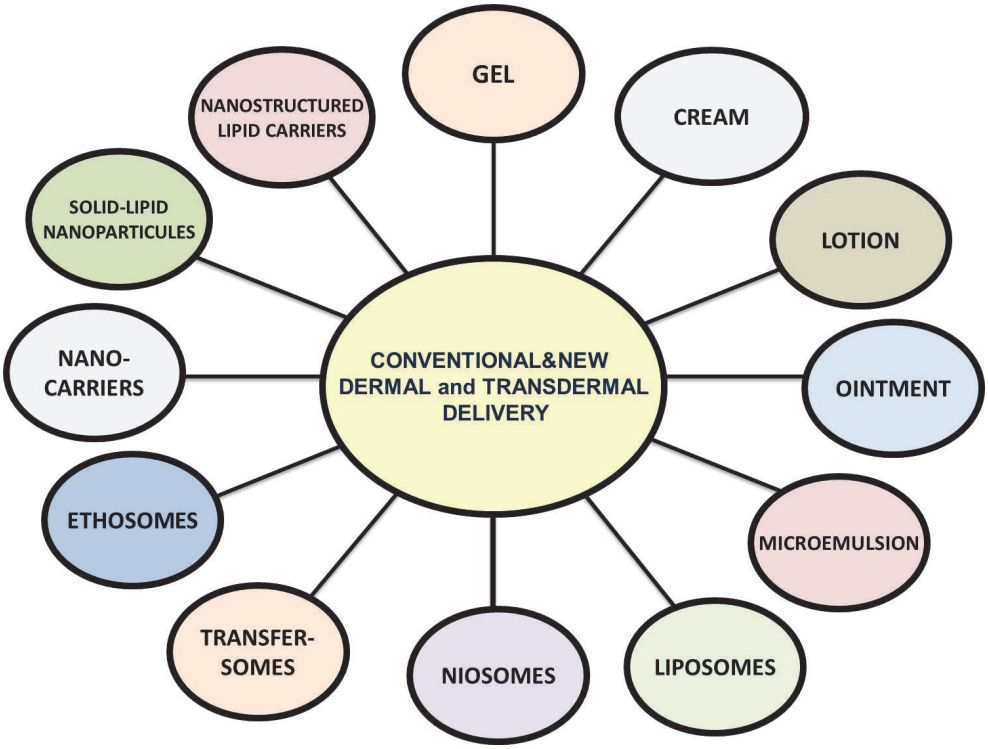


Fig. 1. Schematic representation of the novel and conventional dermal drug delivery systems.

4.1 Conventional formulations

The classical dosage forms of NSAIDs for dermal use that are commercially available are usually gels, creams, ointments and lotions. Table 4 gives a list of NSAIDs which have commercial dermal preparations.

NSAIDs	Formulation type
Benzydamine	Gel, cream
Felbinac	Gel
Bufexamac	Cream, ointment, lotion, emulgel
Diclofenac epolamine	Patch
Diclofenac sodium	Gel, spray gel
Diclofenac potassium	Gel
Diclofenac diethylammonium	Gel, emulgel
Etofenamate	Gel, cream
Ibuprofen	Gel, cream
Ketoprofen	Gel
Naproxen	Gel
Nimesulide	Gel
Piroxicam	Gel
Salicylic acid	Cream, ointment, lotion

Table 4. Commerical dermal formulations of NSAIDs (Micromedex, electronic version, Rx MediaPharma 2011).

4.1.1 Gels

They are two-component semi-solid drug carriers that contain high levels of fluid and viscosity enhancing agents. Polar solvents such as water and alcohol are used in the liquid phase. They contain appropriate viscosity enhancers depending on the physicochemical properties of drug molecule and its compatibility with the vehicle. Simple gels are prepared with a natural polymer, such as carrageen, pectin or sodium alginate, or semi-synthetic stabilizers like cellulose derivatives or synthetic stabilizers like Carbomers (Williams, 2003). As can be seen on Table 3, gel formulations of most of NSAIDs are commercially available because gels are easy to administer, forming a thin film coating on the skin and ensuring rapid action without giving an oily feeling. They are preferred by patients due to these advantages. Besides they are cost-efficient since formulation inputs are less, and they are preferred by manufacturers. Although there are not commercially available dermal formulations of NSAIDs there are studies on development of gel-type formulation of tiaprofenic acid (Okyar et al., 2008 and 2010), meloxicam (Martinez et al., 2007; Jain & Pathak, 2010; Gupta et al., 2002), aceclofenac (Dua et al., 2010) and flurbiprofen (Minghetti et al., 2003; Pandey et al., 2009).

4.1.2 Ointments, creams and lotions

Ointments are semi-solid preparations administered on the skin. Their formulations contain high levels of oil. Typically they have an occlusive action on the skin, and are used for dry lesions. Creams have an emulsion structure although they are defined as semi-solid carrier systems. Emulsions are systems consisting of two phases containing water and oil, where one is disperse in the other. Creams are more acceptable for patients as they have lower viscosity than ointments and are less oily. Lotions are creams with less viscosity (Williams, 2003). There are cream and/or ointment-type preparations of benzydamine bufexamac,

etofenamate, ibuprofen and salicylic acid that are commercially available. Lotion-type preparations of bufexamac and salicylic acid are used in treatments (Table 4).

4.2 Novel formulation approaches for improving skin delivery of NSAIDs

4.2.1 Micromemulsions

Microemulsions are transparent liquid dispersions with a droplet size of 20-200 nm. Their formulations include four fundamental components, which are water, oil, surfactant and co-surfactant. The advantages of microemulsions include enhancing solubility of drugs, thermodynamic stability, ease of preparation and low costs (Neubert, 2011). Microemulsions have recently attracted attention in enhancing dermal permeation of lypophilic drugs as well as hydrophilic drugs. The oils and surfactants included in the composition of microemulsions also act as penetration enhancers. Besides, the composition of formulation and the internal structure of phases enhance diffusion of the drug inside the carrier and improve the partition of drug to SC (Kogan & Garti, 2006). The most important disadvantage of microemulsions is potential risk of skin irritation due to their high content of surfactants. Kantarcı et al. (2007) prepared microemulsion formulations containing diclofenac sodium, and optimized it in with vitro tests. The irritant effect of formulations was investigated on healthy volunteers, and their safety was demonstrated. In another study, lecithin microemulsions of ketoprofen were developed (Paolino et al., 2002). Permeation of drug from microemulsion formulation was compared to the conventional dermal ketoprofen formulation. In this study performed with healthy volunteers, it was demonstrated that ketoprofen microemulsions enhanced the permeation of drug and has good skin tolerability (Amrish & Kumar, 2009). Dalmora et al. (2001) administered microemulsions loaded with piroxicam to rats in vivo, and demonstrated that dermal anti-inflammatory effect was extended, and inflammation inhibition lasted for nine days following single-dose administration. In vivo anti-inflammatory activity study has also demonstrated that microemulsions containing flurbiprofen performed better than conventional gel formulation (Ambade et al., 2008). In another study, nano/submicron emulsions of flurbiprofen were suggested as dermal carriers (Fang et al., 2004).

4.2.2 Vesicular carriers

Vesicular systems such as liposomes, niosomes and transfersomes have been developed for optimization of dermal penetration of drugs and particularly for dermal targeting. Vesicular systems have the advantages of controlling release rate of the active ingredient and to ensure localization of dermally administered drugs in dermal layers. Besides, transdermal administration of vesicular systems helps to carry drug molecules into systemic circulation (El Sayed et al., 2007; Ceve, 2004).

4.2.2.1 Liposomes

Liposomes are described as lipidic vesicles containing water. Cholesterol and phospholipids or amphiphilic ingredients of these compounds are typically used as lipids. Liposomes can capture hydrophilic molecules or contain lipophilic molecules in their membranes. Some liposomes can be adsorbed in the skin surface or may go into fusion. Fusion of liposomes may increase the drag force required for permeation of the molecule and facilitate dermal

penetration of the drug. However, fusion of liposomes on the skin surface does not apply for macromolecular drugs. Another mechanism is penetration of liposomes to SC before fusion with SC lipids and releasing the drug there. With this mechanism, particularly the drug in liposomes that are dermally administered can be localized in different layers of the skin (El Magraby et al., 2008; Williams, 2003).

Mezei & Gulasekharam (1980) used liposomes as "dermal drug carrier system" for the first time. However, liposomes are localized in the outermost layer of the skin (SC). Therefore, it is advantageous in cases where retaining drug in SC is desirable. It does not seem possible with these systems to penetrate the drug to deeper tissues of the skin or into systemic circulation. Therefore, it is rather preferred to increase dermal moisture for cosmetic purposes (El Magraby et al., 2008; Williams, 2003).

4.2.2.2 Niosomes

Niosomes are liposomes prepared with non-ionic surfactants. Dermal penetration of niosomes depend on i) potential penetration-enhancing activity of surfactants in its content, ii) penetration of the vesicle to SC, iii) accumulation of vesicle on the skin surface and/or increasing thermodynamic activity of the drug on the skin surface. These mechanisms depend on the physicochemical properties of the drug, the vesicle and the lipids used (Choi & Maibach, 2005; Williams, 2003). Niosomes are the vesicular systems that are most studies in dermal and transdermal formulations of NSAIDs. This is because niosomes prevent transepidermal water loss, and they act on the lipid structure in the intracellular domain with the effect of high amount of surfactant in their content and overcome the barrier characteristic of the SC layer.

It has been observed that dermal retention and dermal penetration of the drug was enhanced with dermally administered noisome formulation of nimesulid. Besides, it has been determined that the noisome formulation has a faster anti-inflammatory activity than the commercial gel formulation (Shahiwala & Misra, 2002). Manosroi et al. (2008) obtained a higher flux of the drug in SC and deeper dermal tissues (live epidermis and dermis) with elastic noisome formulations loaded with diclophenac diethylammonium. Niosome-like vesicles consisting of hydrated mixtures of cholesterol and non-ionic surfactants are defined as "proniosomes" (Alsarra et al., 2005; Ammar et al., 2011). Alsarra et al. (2005) demonstrated that proniosomes of ketorolac improves permeation of the drug and shortens its lag time. In another study, formulations of proniosome were developed for transdermal delivery of tenoxicam. It has been stressed that proniosome formulation loaded with tenoxicam had higher anti-inflammatory and analgesic effect than the commercially available tenoxicam tablets (Ammar et al., 2011).

4.2.2.3 Transfersomes

Transfersomes are defined as elastic vesicles that can be highly deformed. They are the first generation of elastic vesicles that contain phospholipids and an edge activator. Classical liposomes have a diameter varying from 200 to 400 nm, which is too large to pass through SC. However, transfersomes reach deeper dermal tissues and even the systemic circulation with their elasticity and highly deformable structure (Benson, 2009). It has been demonstrated that as classical liposomes cannot be deformed in the same way, transfersomes ensure higher skin permeation than liposomes in an in vitro comparison of skin permeation of transfersomes and liposomes loaded with meloxicam (Duangjit et al.,

2011). In the same study, the structure of the skip was studied after administration of transfersomes, and it has been found that the structure of lipids in SC was disrupted.

4.2.2.4 Ethosomes

Ethosomes contain phospholipids like classical liposomes; however, they also contain high levels of alcohol. It has also been demonstrated that its components can reach deeper layers of the skin or enter into systemic circulation. Action mechanisms of these carriers in improving permeation is explained by their alcohol content as penetration enhancers as well as disruption of intercellular lipid structure of SC by the phospholipids in their content (Godin & Touitou, 2003; Williams, 2003). Barupal et al. (2010) prepared ethosomes to investigate dermal administration of aceclofenac. They demonstrated that ethosomes have a high drug loading capacity and a good stability.

4.2.3 Nano carriers (Solid lipid nanoparticles-SLN, nanostructured lipid carriers-NLC, and nanocapsules)

It is observed that SLN and NLC formulations have been developed in the last decade for their desirable properties in terms of transdermal administration. SLN are water-in-oil emulsions containing solids as oil phase, and are prepared from solid lipids or from blends of these lipids. NLCs are new generation lipid particles, which have been developed to overcome certain disadvantages of SLNs, such as limited drug loading capacity, gellification risk and drug leakage due to lipid polymorphism during storage. NLCs contain mixtures of different solid lipids blended with liquid oils. The most important advantage of these carriers is their low risk of toxicity. Small size of lipid particles ensures close contact with SC, and may enhance dermal penetration of drug.

Polymeric nanoparticles are also prepared from biologically degradable or non-degradable polymers. The ability of polymeric particles to improve penetration of drugs and their dermal/transdermal applications to target accumulation in different layers of the skin are studied. However, dermal/transdermal administration of polymeric particles have been less studied than lipidic particles. Table 5 summarizes the studies in the literature on nano-carriers of NSAIDs that are dermally and transdermally administered.

4.2.4 Transdermal patches

Transdermal patches are drug carriers that contain an adhesive layer and ensure access of drugs to systemic circulation with controlled release rate. Additionally, the adhesive layer provides a firm contact for the drug to the skin. In general, transdermal patches are classified into two main groups by their methods of formulation, which are membrane-type (reservoir type) and matrix-type. In the former formulation, drug is contained in the adhesive and the drug release rate is controlled by the membrane. In the latter, drug molecules are dispersed or dissolved in polymer matrix. In cases where the matrix is not self-adhesive, a special adhesive layer is added. In transdermal patches, formulation components should be compatible with the skin, and they should be chemically stable and appropriate for use in combination (Padula et al., 2007; Vasilev et al., 2001; Williams, 2003). Among NSAIDs, adhesive types of transdermal patch formulations of meloxicam have been developed and evaluated in vitro/in vivo (Ah et al., 2010). In vivo anti-inflammatory activity of the formulation was compared to the piroxicam patch using adjuvant arthritis model. In conclusion, the meloxicam patch had a better anti-inflammatory effect. In another

study, pharmacokinetic data obtained with dermally administered ketoprofen patch was compared to the data of gel formulation. The obtained plasma level of ketoprofen was demonstrated to be higher than the gel formulation (Mazieres, 2005).

NSAIDs	Nano carrier	Results	Refs
Celecoxib	NLC based gel	Gel formulations of celecoxib prepared with NLC exhibited fasted drug input and sustained anti-inflammatory activity up to 24 h.	Joshi & Patravale, 2008
Flufenamic acid	Poly(lactide-co-glycolide) nanoparticles	Nanoencapsulation of flufenamic acid has significantly increased drug transport and accumulation in the skin.	Luengo et al., 2006
Flurbiprofen	NLC	NLC formulation of flurbiprofen was led to the increase in drug permeation with respect to its conventional solution.	Gonzales-Mira et al., 2011
Flurbiprofen	SLN	SLN dispersion and gel formulation showed a sustained drug release over 24 h period.	Jain et al., 2005
Indomethacin	NLC	Prolonged in vivo anti-inflammatory activity of indomethacin was observed with NLC hydrogels compared to its aqueous solution and hydro-alcoholic gel.	Ricci et al., 2005
Indomethacin	Nanocapsule	Transdermal delivery of indomethacin with poly n-butylcyanoacrylate nanocapsules was improved with respect to conventional gel formulation.	Miyazaki et al., 2003
Ketoprofen	SLN	Ketoprofen loaded SLN formulations showed a prologed anti-inflammatory effect compared to its solution.	Puglia et al., 2008
Ketorolac	NLC	NLC formulation of ketorolac exhibited a sustained drug release pattern due to form a drug reservoir into skin. **requires rewriting**	Puglia et al., 2006
Nimesulide	Nanocapsule /nanoemulsion / nanospheres	Nimesulide-loaded nanocarriers formulated in hydrophilic gels exhibited good physico-chemical properties for its dermal administration.	Alves et al., 2005
Nimesulide	Nanocapsule /nanoemulsion / nanospheres	Following the application of gel formulations of nimesulide based on nanocarriers was detected viable epidermis compared to conventional gel formulations.	Alves et al., 2005

Table 5. Studies on the development of nanocarriers of NSAIDs to improve their skin permeability.

5. Conclusions

During the last two decades, skin has been shown to be a suitable delivery site for drugs that are formulated dermally. Researchers have been trying to overcome gastrointestinal side effects by dermal and transdermal delivery of NSAIDs. Dermal administration of

NSAIDs enables local drug delivery to diseased tissues and obtains high drug concentration in the application site. Dermal application seems to offer an alternative application route for preventing systemic side effects of NSAIDs. However, SC is a highly effective barrier and challenging for absorption of drugs through skin and drugs may not accumulate properly in the target tissues. The most popular strategy is to include chemical enhancers into dermal and transdermal formulations to enhance skin delivery of drugs. However, it is difficult to choose a penetration enhancer, and to date no penetration enhancer has been proven to be ideal. Another approach to improve skin permeation is to develop novel drug carrier systems of NSAIDs, in addition to the conventional dosage forms. Microemulsions and nano carriers are the most frequently preferred carrier systems for NSAIDs. These new carrier systems ensure drug permeation to deeper layers of the skin and reach the synovial fluid. These new drug delivery approaches are jointly aiming at minimizing drug dose, diverting drugs to the target tissue, and enhancing efficacy in patients. The findings seem to be promising and it can be anticipated that the commercial novel carrier systems, providing localization of drugs in viable epidermis and dermis layers of skin, could come into the market. Thus, by employing these novel systems we may achieve a critical leap forward in the safe administration of NSAIDs.

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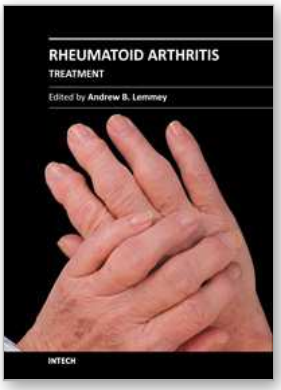

Rheumatoid Arthritis - Treatment

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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821