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13.1 Ion-Pair Formation for Penetration Enhancement

A diffusing molecule has to cross the skin barrier composed of the highly lipophilic stratum corneum (SC) and the hydrophilic viable epidermis (ED) in order to reach the deep skin layer as well as the layers under the skin. Therefore, only active compounds with ideal physicochemical properties, e.g., low molecular weight, suitable solubility in oil and water, moderate partition coefficient, and low melting point, can permeate through both the lipid and polar microenvironments in the skin (Barry 2001). Obviously, hydrophilic ionized drugs do not readily distribute into or penetrate through the lipophilic SC membranes. On the contrary, the problem for those very lipophilic drugs, which can easily distribute into SC membranes, is that they do not readily translocate from the SC to the relative hydrophilic ED due to their high solubility in the intercellular lipids, thus limiting their skin permeation. Ion pairing provides a possible approach to adjust the physicochemical properties of drugs without any changes on the structure and pharmacologic actions of the drug compound and consequently facilitate the penetration of drugs across the skin barrier (Neubert 1989). Some products using ion-pair technique, such as Flector[®] Patch (diclofenac epolamine topical

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patch) from IBSA Institut Biochimique SA (Switzerland) and Voltarol[®] emulgel (diclofenac diethylamine emulgel) from Novartis Consumer Health UK Ltd. (UK) are commercially available.

13.1.1 The Concept of Ion Pairs

An ion pair is defined as neutral species which consists of a pair of oppositely charged ions held together by coulomb attraction without formation of a covalent bond (McNaught and Wilkinson 1997). Practically, an ion pair behaves as one unit in determining conductivity, kinetic behavior, osmotic properties, etc.

In 1926, Bjerrum developed a theory that took the interaction of ions into account. He introduced, for the first time, the concept of ion pairs and showed how the mass action constant of the equilibrium between ions and ion pairs is dependent on the dielectric constant of the solvent as well as on temperature and the size of the ions (Kraus 1956). According to the Bjerrum theory, oppositely charged ions with their centers closer together than a distance (q) (pm) are considered to constitute an ion pair:

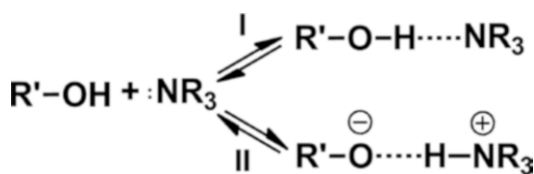
$$q = 8.36 \times 10^6 z^+ z^- / (\epsilon_r T) \quad (13.1)$$

Where z^+ and z^- are the charge numbers of the ions, ϵ_r is the relative dielectric constant of the medium and T is the absolute temperature. The resulting ion pairs exhibit stable, thermodynamically distinct species. Depending on the strength of the solvent–ion interactions, ion pairs can be classified into two types: contact (tight, intimate) and solvent-separated (loose) ion pairs (Nagy and Takacs-Novak 2000).

In polar solvents with high dielectric constant such as water, ion-pair formation is also possibly obtained. Diamond (1963) demonstrated that the existing of so-called hydrophobic ion pairing (HIP). HIP is composed of two large hydrophobic ions self-assembled together by coulomb attraction, hydrophobic forces, and hydrogen bonding in polar solvents. Even though the HIP complexes display enhanced lipophilicity and thus are more suited for their potential application,

it has not been paid extensive attention yet compared to the classical ion pairs mentioned above.

Hydrogen-bonded ion pairs are a special type of ion pairs. The concept of hydrogen-bonded ion pairs was brought out for better understanding the nature of the protonic acid–base interaction occurring in non-dissociating solvents (Barrow 1956). The interaction between sufficiently strong protonic acids and bases in a solvent environment, especially in solvents with low dielectric constant, tends to promote the formation of ion pairs accompanied by proton transfer of a hydrogen bond. According to the Brønsted-Lowry concept of acids and bases in aprotic solvents, two forms of simple prototropic equilibrium exist as follows (Hudson et al. 1972):



The classical electrostatic attraction was predominant in weak hydrogen bonds, so-called classical hydrogen bonds (Equilibrium I). However, on going to stronger hydrogen bonds, the contribution of the proton transfer led to the formation of ion pairs, so-called hydrogen-bonded ion pairs (Equilibrium II) (Arunan et al. 2011; Ratajczak 1972). Such a hydrogen bond is extremely polarizable. The formation of a hydrogen-bonded ion pair between a carboxylic acid and a pyridine base in benzene solution is a typical example of acid and base interaction (Barrow 1956).

13.1.2 Molecules Suitable for Ion-Pair Formation

Both drugs and counter ions have to meet certain demands in order to form ion pairs successfully. For hydrophilic ionized drugs, Neubert (1989) pointed out that the ideal counter ions needed to possess high lipophilicity, sufficient solubility in physiological compatibility, and metabolic stability, which was suitable for ion-pair formation and crossing lipid membranes in

the form of ion pairs. The ion pairs formed by quaternary ammonium drugs and organic anions are typical examples of ion-pair formation (Takacs-Novak and Szasz 1999). Similarly, Miller et al. (2009) performed a study in which three lipophilic acidic counter ions were employed to give an understanding of the mechanism of ion-pair mediated membrane transport of low permeable drugs.

Besides ionized species, for stronger hydrogen bonds like $\text{OH}\cdots\text{N}$, the contribution of the proton transfer, $\text{OH}\cdots\text{N}\rightleftharpoons\text{O}^-\cdots\text{HN}^+$, could lead to a hydrogen-bonded ion-pair formation. Sobczyk and Paweła (1974) have demonstrated the existence of proton-transfer equilibrium under appropriate conditions by measuring the dipole moment of carboxylic acid–pyridine base complexes. The results indicated that the dipole moments of these complexes were dependent on the $\text{p}K_a$ difference ($\Delta\text{p}K_a$) between carboxylic acid and pyridine base, and large dipole moment was induced by strong interaction of ion pairs. This type of interaction depends on the following factors: (a) $\Delta\text{p}K_a$ of protonic acid and base, (b) specific complex solvation by solvent molecules, and (c) the influence of solvent expressed by its macroscopic dielectric permittivity. Based on the ion-pair model established by Huyskens and Zeegers-Huyskens (1964), it was predicted that a $\Delta\text{p}K_a$ of 3.6–6 between protonic acid and base could lead to an almost complete shift to the proton-transfer equilibrium. A recent study (Gilli et al. 2009) also showed that ion-pair formation could be reliably predicted from $\Delta\text{p}K_a$ between the donor and acceptor groups.

13.1.3 The Confirmation of Ion-Pair Formation

In theory, ion pairs are defined as binary species which exist in solution and in solid in the salt form. Such intermolecular interaction can be qualitatively inferred from the spectral characteristics. A variety of spectroscopic techniques including infrared spectroscopy (IR), nuclear magnetic resonance (NMR), ultraviolet–visible spectroscopy (UV-Vis), electron spin resonance

spectroscopy (ESR), and X-ray crystallography could provide insights into ion-pair formation.

IR and NMR spectroscopy often offer experimental proofs to directly indicate the formation of ion pairs, and they are especially pronounced for hydrogen-bonded ion pairs (Barthel and Deser 1994; Biliškov et al. 2011; Habeeb 1997; Pregosin 2009). Recently, by using IR and chemical exchange two-dimensional infrared (2DIR) spectroscopy, Lee et al. (2011) investigated the contact ion pairs (CIP) assembled by Li^+ and SCN^- ions in *N,N*-dimethylformamide. In IR spectrum, the CIP formation led to a blue shift ($\sim 16\text{ cm}^{-1}$) of the CN stretch frequency of Li-SCN CIP with respect to that of free SCN^- ion. Moreover, the temperature-dependent IR absorption spectra revealed that the CIP formation was an endothermic process. The CIP association and dissociation time constants (165 and 190 ps, respectively) were determined by chemical exchange 2DIR spectroscopy. The experimental results indicated that the ion-pair formation was a dynamic process in electrolyte solutions and in biological systems under physiological conditions. In the case of hydrogen-bonded ion pairs, a broad continuum, called as the Zundel continuum, is often observed in IR spectrum with extensive intermolecular hydrogen bonding, for which proton transfer is valuable. The broad band is caused by the strong hydrogen bonds in which a proton is distributed between the two hydrogen-bonded species by tunneling (Biliškov et al. 2011). According to the classical theory of hydrogen bond, a shift toward lower fields in the NMR spectrum is suggested as a criterion to confirm the formation of a hydrogen bond due to strong deshielding of the protons. Xi et al. (2012a, b) confirmed the formation of hydrogen-bonded ion pairs between weak acidic drugs and organic amines at 1:1 molar ratio by IR and $^1\text{H-NMR}$. In this study, teriflunomide (TEF) and lornoxicam (LOX), two weak acidic drugs with OH groups, were used as the model drugs, and various organic amines including triethylamine (TEtA), diethylamine (DEtA), *N*-(2'-hydroxyethanol)-piperidine (NP), diethanolamine (DEA), and triethanolamine (TEA) were employed as the

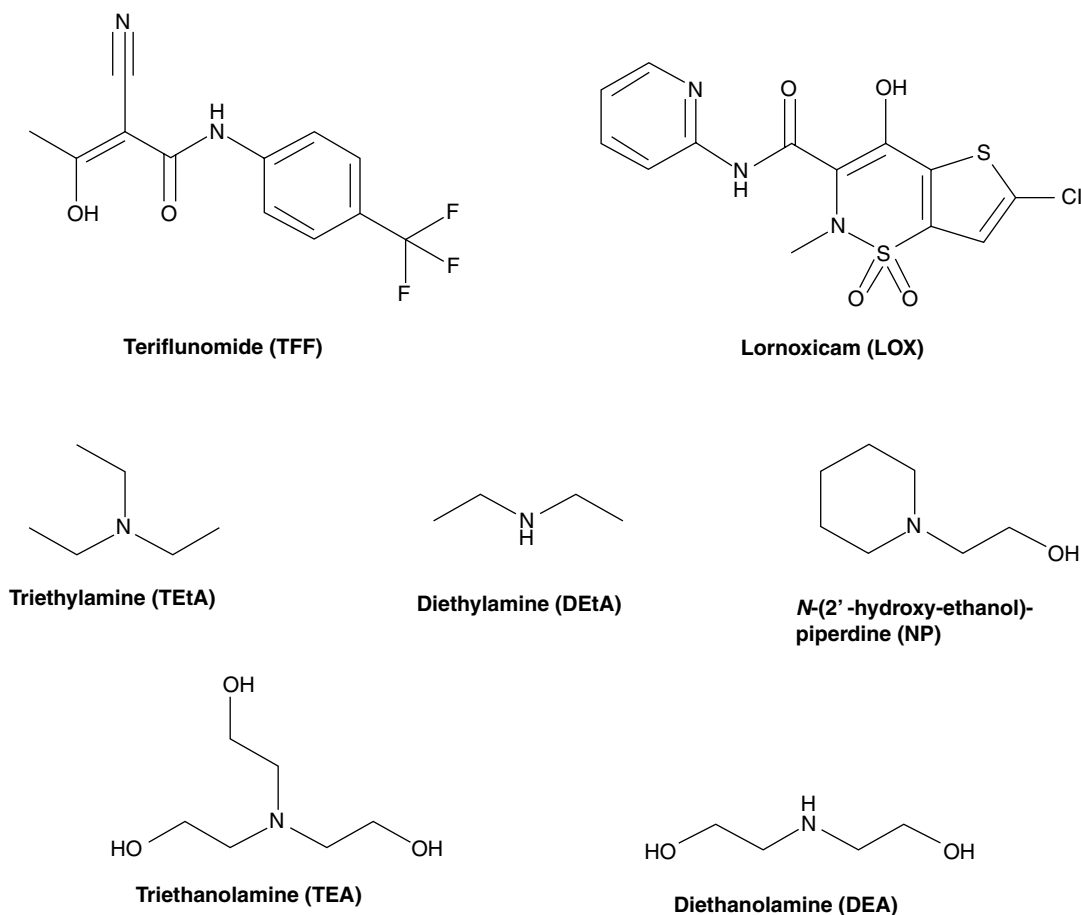


Fig. 13.1 The chemical structure of teriflunomide (TEF), lornoxicam (LOX), triethylamine (TEtA), diethylamine (DEtA), *N*-(2'-hydroxyethanol)-piperidine (NP), diethanolamine (DEA), and triethanolamine (TEA)

counter ions, whose structure was shown in Fig. 13.1. CHCl_3 and CDCl_3 solutions of TEF or LOX with or without the adding of equimolar organic amines were detected, respectively, by spectroscopic methods. In IR spectra (Fig. 13.2), the absorption at $\sim 3,400\text{ cm}^{-1}$ was assigned to stretching vibration of OH group of the two drugs. A continuum gave rise to a very broad absorption in the $3,300\text{--}2,000\text{ cm}^{-1}$ range in the presence of most of organic amines. In $^1\text{H-NMR}$ study, compared to the signal of the proton from OH group of TEF or LOX itself (15.35 and 13.02 ppm, respectively), the proton magnetic resonance of OH in the complexes has moved toward higher field, as illustrated in Fig. 13.3. It seemed that the results were contradictory to the abovementioned classical theory

of hydrogen bond in NMR. However, actually this phenomenon may be caused by strong shielding of the proton, which was a direct consequence of the intermolecular hydrogen bond interaction between drugs and organic amines instead of intramolecular hydrogen bonds in drugs. Notably, the chemical shift of OH group kept almost constant when the stoichiometric ratios of drug to organic amine were varied from 1:1 to 1:100. These results suggested that TEF and LOX have been integrated sufficiently into ion pairs at the equimolar ratio.

In addition, UV-Vis, ESR spectra in solution, and X-ray crystallography also have been employed for measuring the electronic changes in ion-pair formation process (Lü et al. 2005;

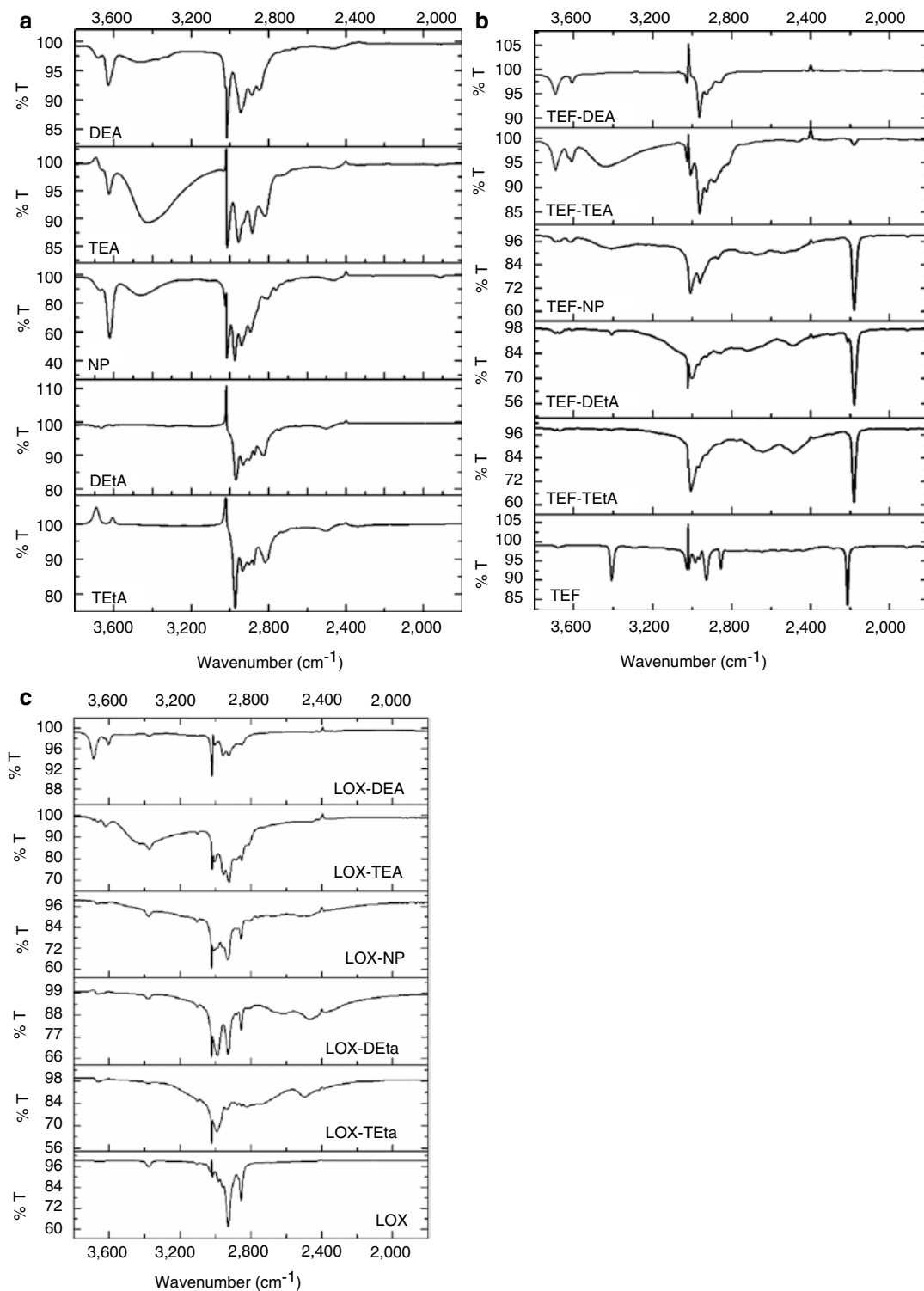
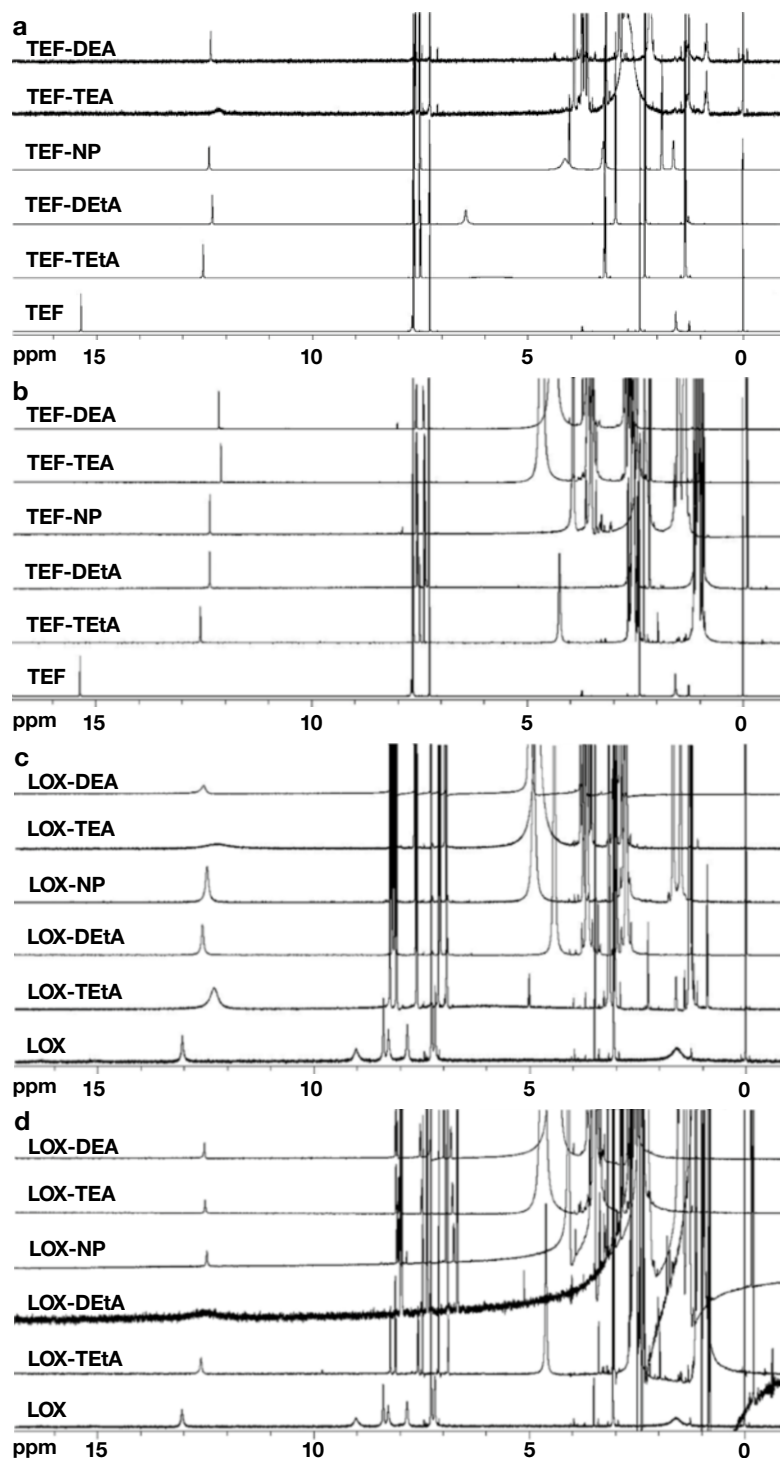


Fig. 13.2 Infrared spectra of organic amines, TEF and LOX in CHCl_3 : (a) organic amines which was equimolar with test drug; (b) TEF with or without equimolar

organic amines; (c) LOX with or without equimolar organic amines

Fig. 13.3 $^1\text{H-NMR}$ spectra of TEF and LOX with or without organic amines in CDCl_3 , at different molar ratios: (a) TEF, amines = 1:1; (b) TEF, amines = 1:100; (c) LOX, amines = 1:1; (d) LOX, amines = 1:100



Pal et al. (2010). Hudson et al. (1972) found that when weak acidic 3,4-dinitrophenol encountered organic amines at different molar ratio, a series of characteristic bathochromic shifts in UV

absorption spectra were presented in going from free acid to a hydrogen-bonded complex, to an ion pair, to a solvated ion pair or a solvated anion. Lü et al. (2005) determined the crystal structures

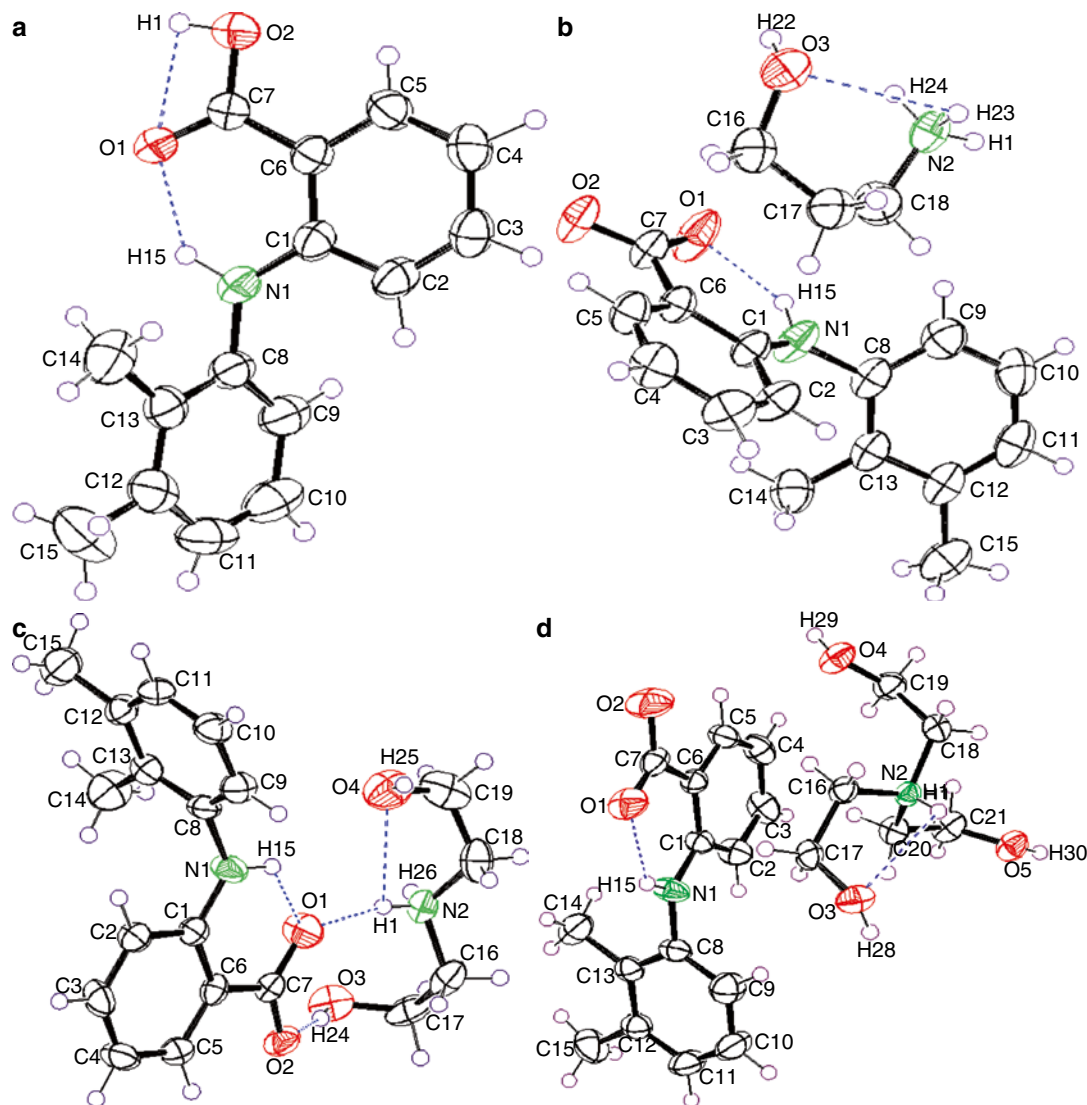


Fig. 13.4 Stereoscopic view of (a) MH, (b) MH-propanolamine, (c) MH-DEA, and (d) MH-TEA, showing atom numbering, 50 % thermal probability ellipsoids, and

hydrogen bonds. Dashed lines indicate the intermolecular hydrogen bonding

of pure ion-pair salts $K(L_C)^+/DNB^-$ and $K(L_E)^+/DNB^-$ by X-ray crystallography. In the near-IR spectral analysis, they found that there were the same patterns of vibronic progressions for distinguishing the “separated” from the “contact” ion pair in both of the crystalline solid state and THF solution state, which ensured that the same X-ray structures persist in solution. Most importantly, in this study, the labilities of these dynamic ion pairs in solution were thoroughly elucidated by the temperature-dependent ESR

spectral changes. Compared with other methods, X-ray crystallography can provide definitive structural information via analyzing the diffraction pattern of single crystal ion-pair salts. In another study, Fang et al. (2004) prepared the crystals of ion-pair complexes with an equimolar ratio of mefenamic acid (MH) and alkanolamines by removing the solvent in vacuo and subsequently confirmed that these complexes were associated with hydrogen bonds using X-ray crystallography (Fig. 13.4).

13.1.4 The Effect of Ion-Pair Formation on Skin Permeation

13.1.4.1 The Mechanism of Skin Penetration Enhancement by Ion-Pair Formation

The effect of ion-pair formation on skin permeation is complex, and its mechanism has not been thoroughly clarified. Generally, the skin penetration enhancement by ion-pair approach with suitable counter ions is mainly dependent on the physico-chemical properties of the counter ions (e.g., lipophilicity, pK_a , and structure) and the solubility of ion pairs in donor medium.

The extent of penetration enhancement by ion-pair formation is strongly related to the lipophilicity of the ion pairs and the properties that depend on the lipophilicity of the selected counter ions. A series of studies performed by Neubert et al. (Neubert et al. 1984; Neubert and Dittrich 1989; Neubert and Fischer 1991) have made great contribution to the understanding of how hydrophilic ionized drugs penetrate across lipid membranes together with lipophilic counter ions. These studies showed that the partition coefficient of the hydrophilic drugs, buformine, quinine, pholedrine, and bretylium, was markedly increased by more than twofold after the formation of ion pairs with lipophilic ions, and thereby the transport of ionized drugs across an artificial lipid membrane (dodecanol collodion membrane) could be enhanced. Moreover, it was found that the counter ions could be accumulated in the lipid membrane due to their high lipid solubility and that they acted as carriers for the ionized drugs. Besides the increased transport of ionized drugs, the counter transport of protons and lithium ions, respectively, was also observed. Nam et al. (2011) also provided a similar result in the skin permeation of hydrophilic and highly ionized risedronate (RIS) with three lipophilic basic counter ions, L-arginine, L-lysine, and diethylenetriamine, at different molar ratios. To varying degree, all the counter ions could enhance the solubility of RIS in xylene, a lipophilic solvent. Although RIS ion pairs are slightly unstable in the aqueous solution, they had a remarkable

enhancing effect on RIS penetration from the aqueous solution into hairless mouse skin, and RIS-diethylenetriamine ion pair brought out the largest enhancement ratio (ER), up to 36-fold compared to only RIS.

As to lipophilic drugs possessing some polar functional groups, e.g., $-\text{COOH}$, $-\text{OH}$, and $-\text{NH}_2$, their skin permeation can also be enhanced by hydrogen-bonded ion-pair formation (Cheong and Choi 2002; Green et al. 1989; Kamal et al. 2007; Nogueira et al. 2011). However, for those lipophilic drugs, their lipophilicity can be decreased by ion-pair formation with small molecular weight relative hydrophilic counter ions (Fang et al. 2003). The effect of the organic amines including monoethanolamine (MEA), DEA, TEA, and propanolamine (PPA) on the penetration of mefenamic acid (MH) across hairless rat skin from the lipophilic mixed solvent of isopropyl myristate (IPM) and ethanol (9:1). The *n*-octanol/water partition coefficients ($\log K_{o/w}$) at 32 °C of MH and its corresponding ion pairs, MH-MEA, MH-DEA, MH-TEA, and MH-PPA, were 3.31, 0.79, 0.74, 1.99, and 0.66, respectively, which indicated that these complexes were relatively hydrophilic compared with MH. Hence, the transdermal delivery of MH was significantly enhanced by the formation of hydrogen-bonded ion pairs, and the ER values of these ion pairs were 279, 48, 84, and 357, respectively. Obviously, the reduced lipophilicity of the complexes has facilitated the partition from the SC to the ED and consequently enhanced drug delivery through the skin. These results suggested that a major part of ion pairs remained the integrity of ion pair during the process of crossing the lipophilic SC and the hydrophilic ED until they reach the receptor compartment. The subsequent studies done by Fang's group further confirmed this point of view (Table 13.1).

In donor medium, the pK_a of the counter ions is another main factor that influences the skin permeation of ion pairs, especially the hydrogen-bonded ion pairs. A positive correlation was found between the skin permeation of ion pairs and the pK_a of the counter ions was found (Ma et al. 2010; Xi et al. 2012a, b). In other words, the ΔpK_a between the drug and the counter ion (they are acids and bases,

Table 13.1 The enhancement ratio (ER) of ion pairs of drugs with different amines

Drugs	Counter ions	ER ^a
Teriflunomide in isopropyl palmitate ^b	None	1.00
	Diethylamine	2.47
	Triethylamine	12.69
	Triethanolamine	1.44
	Diethanolamine	1.15
	<i>N</i> -(2'-hydroxyethanol)-piperidine	4.54
Lornoxicam in isopropyl palmitate ^c	None	1.00
	Diethylamine	13.63
	Triethylamine	19.52
	Triethanolamine	4.92
	Diethanolamine	13.77
	<i>N</i> -(2'-hydroxyethanol)-piperidine	12.08
Flurbiprofen in 10 % EtOH/isopropyl myristate ^d	None	1.00
	Diethylamine	2.02
	Triethylamine	2.27
	Triethanolamine	2.93
	Diethanolamine	3.76
	Ethanolamine	2.60
<i>N</i> -(2'-hydroxyethanol)-piperidine	1.86	
Glipizide in 20 % EtOH/isopropyl myristate ^e	Na salt	1.00
	Diethylamine	6.79
	Triethylamine	19.61
	Triethanolamine	2.34
	Diethanolamine	5.77
	Ethanolamine	11.92
<i>N</i> -(2'-hydroxyethanol)-piperidine (NP)	3.90	

^aER, the enhancement ratio of the cumulative amounts of drug permeated between with and without organic amines

^{b,c}Xi et al. (2012a, b)

^dMa et al. (2010)

^eTan et al. (2009)

correspondingly) can directly influence the strengths (stability) of hydrogen-bonded ion pairs in a nonpolar medium.

Most intermolecular hydrogen bonds in the liquid state are formed and broken on an extremely short timescale (e.g., $\sim 10^{-5}$ s), even a picosecond scale (Becker 2007; Simon and Peters 1982). It has been widely accepted that there are abundant hydrogen bond acceptors and donors existing in the SC part of the skin and they may disturb the binding of ion pairs and further influence the

stability of hydrogen bonds (Guy and Hadgraft 1984; Michaels et al. 1975). According to Xi et al. (2012a, b), the stability parameter of ion pairs (T_{life}) can be obtained, based on the following Eq. 13.2 and data of ¹H-NMR shown in Fig. 13.3.

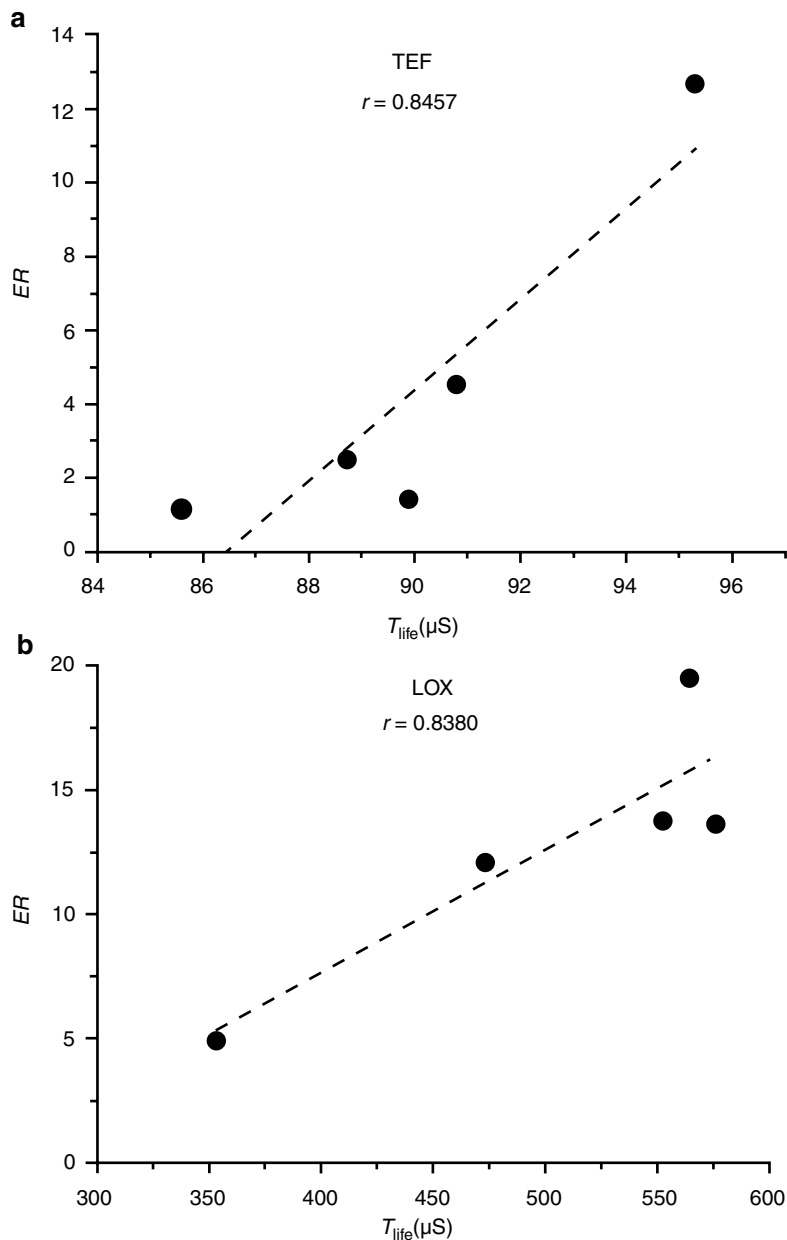
$$T_{\text{life}} > \frac{1}{2\pi(\Delta\delta)\nu_0} \quad (13.2)$$

where ν_0 was the spectrometer frequency and $\Delta\delta$ was the chemical shift difference (Tubbs and Hoffmann 2004). The results in Fig. 13.5 showed that, in general, the ER values were increased with T_{life} . Therefore, the better stability of hydrogen-bond ion pairs notably facilitated transdermal drug delivery.

Megwa et al. (2000a, b) carried out some in vitro studies to evaluate the possibility of improving the skin permeation of salicylate through human epidermis from an aqueous solution by forming ion pairs with basic counter ions (alkylamines and quaternary ammonium ions). The skin permeation of the salicylate ion pairs with primary amines and quaternary ammonium ions was lower than that of salicylate itself (ER < 1), while all of secondary and tertiary amines except DEtA (ER=0.83) significantly promoted the skin permeation of salicylate (ER: 1.34–4.80). The enhancement effect of these amines on the penetration of salicylate was in the following order: quaternary < primary < secondary < tertiary. This phenomenon was attributed to the fact that the complex of salicylate with tertiary amines had higher stability than that with primary or secondary amines.

The skin permeation rate is also dependent on the concentration of the soluble permeant in the applied vehicle. For lipophilic drugs with sparingly solubility in both oil and water like piroxicam, meloxicam, and LOX, the skin permeation is very poor (Cheong and Choi 2002; Xi et al. 2012b; Zhang et al. 2009). Improving the solubility in donor solution and the partition in the SC and the ED by ion-pair formation is the main mechanism of penetration enhancement for those drugs. A recent study (Song et al. 2012) showed that bisoprolol-maleate salt possessed a higher solubility in DURO-TAK[®] 87-4098 acrylate-vinyl acetate

Fig. 13.5 The relationship between the skin enhancement of ion pairs of TEF and LOX and the stability parameter T_{life}



adhesive (National Starch & Chemical Co., USA) than bisoprolol-fumarate salt, which was responsible for the higher penetration enhancing effect of the maleate salt. In addition, ion pairs existing in salt form can obviously decrease the melting point of the parent drug, which is frequently used as a predictor of solubility, and thereby promotes the skin permeation of drugs from transdermal formulations, such as patches and emulgels (Cheong and Choi 2003; Wang and Fang 2008).

13.1.5 Ion-Pair Formation vs. Penetration Enhancers

Currently, the application of chemical enhancers is a frequently used approach to enhance the permeation of drugs through biomembranes. However, chemical enhancers are not omnipotent in the drug delivery across the skin. Tan et al. (2009) found that glipizide (GP) ion pairs with organic amines as the counter ions provided an

Table 13.2 The enhancement ratio (ER) of ion pairs of drugs with different counter ions and penetration enhancers

Drugs	Counter ions	ER ^a	Penetration enhancers	ER
Indapamide in 30 % (w/w) enthol/IPM ^b	None	1.00	None	1.00
	Acetic acid	2.74	5 % Azone [®]	4.83
	Maleic acid	4.34	5 % <i>l</i> -menthol	3.01
	Oxalic acid	2.85	5 % oleic acid	2.52
	Adipic acid	3.10	5 % <i>N</i> -methyl pyrrolidone	3.88
	Lactic acid	8.46		
	Citric acid	3.47		
	Succinic acid	5.13		
	Fumaric acid	6.93		
Scutellarin in 20 % enthol/IPM ^c	None	1.00	None	1.00
	Diethylamine	4.76	5 % Azone [®]	5.64
	Triethylamine	3.83	5 % <i>l</i> -menthol	3.28
	Ethanolamine	7.11	5 % oleic acid	2.60
	Diethanolamine	3.68	5 % <i>N</i> -methyl pyrrolidone	1.38
	Triethanolamine	1.66		
Meloxicam in 10 % propylene glycol /IPM ^d	None	1.00	None	1.00
	Diethylamine	3.71	5 % Azone [®]	2.89
	Triethylamine	1.99	5 % <i>l</i> -menthol	1.28
	Ethanolamine	1.399	5 % oleic acid	2.29
	Diethanolamine	4.20	5 % <i>N</i> -methyl pyrrolidone	5.77
	Triethanolamine	3.94		
	<i>N</i> -(2'-hydroxyethanol)-piperidine	5.78		

^aER, the enhancement ratio of the cumulative amounts of drug permeated between with and without counter ions

^bRen et al. (2007)

^cWang et al. (2008)

^dZhang et al. (2009)

obvious enhancement of the skin permeation of GP, while five common enhancers, IPM, propylene glycol, *N*-methyl-2-pyrrolidone (NMP), Azone[®] (AZ, Tianmen Kejie Pharmaceuticals Co., Ltd., China), and oleic acid (OA), had no enhancing effect. Moreover, Cheong and Choi (2002) investigated the effect of various enhancers on the permeation of piroxicam (PX) and its ethanolamine salts (PX-EAs). The results showed that, in general, ion-pair salts still exerted a great enhancement on the penetration of PX from various saturated solution in which the enhancers also work as the donor mediums. As illustrated in Table 13.2, some studies support the finding that ion-pair formation shows a better or comparable penetration enhancing effect compared to classical chemical penetration enhancers (Ren et al. 2008; Wang et al. 2008; Zhang et al. 2009).

13.2 Complex Coacervates for Penetration Enhancement

Complex coacervates are a specialized form of ion pairs, which represents the separation of an aqueous phase containing a mixture of oppositely charged ions into a dense coacervate oil phase, rich in ionic complex, and a dilute equilibrium phase. The difference between complex coacervates and ion pairs is that a complex coacervate exists as a binary phase system. However, in transdermal delivery systems, complex coacervates behave like ion pairs. Stott et al. (1996) prepared complex coacervates composed of cationic amitriptyline (AMI) and counter ions including sodium deoxycholate (NaD) or sodium lauryl sulfate (SLS). The produced complex

coacervates AMI-NaD and AMI-SLS were employed to investigate their potentials to enhance transdermal flux of AMI. Although AMI-NaD was separated into two distinct phases (octanol and vehicle), while AMI-SLS was in sol state, both of the systems could obviously increase octanol/vehicle partition coefficients of AMI. However, in the skin permeation study, only the AMI-NaD coacervate provided a 2.2-fold increment in drug flux. On the contrary, the AMI-SLS coacervate showed a marked reduction in drug flux. The results indicated that the increased lipophilicity of the coacervate's oil phase could contribute to an increase in the transdermal flux of charged species.

13.3 Summary

In conclusion, ion-pair formation is a simple and useful method for enhancing percutaneous penetration of drugs by modifying the physicochemical properties of parent molecules and by regulating the partition of drugs between the dosage form, the SC, and the ED. Furthermore, hydrogen-bonded ion pairs make some unionizable molecules become suitable for ion-pair formation. In order to obtain a maximum enhancement in permeation of drugs, the combination of ion pairs and penetration enhancers is a feasible approach. The enhancement mechanism of ion pairs in transdermal drug delivery is worth for further study. As to complex coacervates, although the published data about their application in the field of transdermal drug delivery is limited, this technology is still a bright prospect for transdermal pharmaceutical formulations.

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