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Formation of ion-pairs in aqueous solutions of diclofenac salts

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Abstract

In this work we studied the ability of the diclofenac anion to form ion-pairs in aqueous solution in the presence of organic and inorganic cations: ion-pairs have a polarity and hydrophobicity more suitable to the partition than each ion considered separately and can be extracted by a lipid phase. The cations considered were those of the organic bases diethylamine, diethanolamine, pyrrolidine, *N*-(2-hydroxyethyl) pyrrolidine and *N*-(2-hydroxyethyl) piperidine; the inorganic cations studied were Li^+, Na^+, K^+, Rb^+, Cs^+. Related to each cation we determined the equilibrium constant (K_{XD}) for the ion-pair formation with the diclofenac anion in aqueous solution and the water/*n*-octanol partition coefficient (P_{XD}) for each type of ion-pair formed. Among the alkali metal cations, only Li^+ shows some interaction with the diclofenac anion, in agreement with its physiological behaviour of increasing clearance during the administration of diclofenac. The influence of the ionic radius and desolvation enthalpy of the alkali metal cations on the ion-pair formation and partition was briefly discussed. Organic cations promote the formation of ion-pairs with the diclofenac anion better than the inorganic ones, and improve the partition of the ion-pair according to their hydrophobicity. The values of the equilibrium parameters for the formation and partition of ion-pairs are not high enough to allow the direct detection of their presence in the aqueous solution. Their formation can be appreciated in the presence of a lipid phase that continuously extracts the ion-pair. Extraction constants ($E_{XD} = P_{XD} \cdot K_{XD}$) increase passing from inorganic to organic cations. This study could help to clarify the mechanism of the percutaneous absorption of diclofenac in the form of a salt, a route where the formation of ion-pairs appears to play an important role.

Keywords: Association constant; Diclofenac salts; Extraction constant; Ion-pairs; Organic and inorganic cations; Partition coefficient

1. Introduction

A large amount of drugs are weak acids or bases and improve their behaviour in aqueous solutions in the form of salts. In some case a mutual affinity between the cation and the anion

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present in the salt allows the formation of a complex or weakens the ionic dissociation, originating species such as ion-pairs. These species, where ions are in close proximity and their charges are masked or shielded by the low dielectric constant of hydrocarbon moieties of the functional groups, display a lower hydrophilicity than the two ions considered separately and offer unusual behaviour for an ionic species, such as high solubility in apolar solvents or increased partition towards a lipid phase.

Diclofenac, a non-steroidal anti-inflammatory acidic drug, has a high partition coefficient ($\log P = 4.0$), but very low water solubility (17.8 mg/l) in its unionized form: because of these characteristics, it is often administered in salt form. The great hydrophobicity of the parent molecule is partly maintained even when the drug is in the form of a salt. In fact, calculations by means of fragment constant method revealed that diclofenac anion has a positive $\log P = 0.69$ (Fini et al., 1995). Compared to the free diclofenac acid, the solubility values of some diclofenac salts, measured in a silicone membrane or in isopropyl myristate, even low, are far from zero, suggesting a fair affinity of the diclofenac salts towards a hydrophobic phase (Maitani et al., 1994). This result was confirmed by the solubility values measured for some diclofenac salts in a number of solvents (Fini et al., 1994a), including *n*-octanol. In particular the difference in solubility observed for the salt diclofenac/*N*-(2-hydroxyethyl) pyrrolidine in dodecane and *n*-octanol suggested the formation of ion-pairs in this last solvent. Therefore the *n*-octanol/water positive log *P* found for some diclofenac salts was not surprising (Fini et al., 1993). This behaviour can be the consequence of the formation of ion pairs, as was also reported in the case of indomethacin (Inagi et al., 1981).

A recent review (Fini et al., 1996) on the effect of the counter ion in diclofenac salts has highlighted the ability of diclofenac anion to form complex with heavy metal ions, such as Cu^{2+}, Zn^{2+} or Cd^{2+} (Nekroshus and Arzamastev, 1990; Bucci et al., 1993; Kovala-Demertzi et al., 1993, 1997), and also to form ion-pairs in the solid state with hydroxy aliphatic bases (Castellari and Sabatino, 1994; Castellari and Ottani, 1995, 1996, 1997; Castellari and Sabatino, 1996; Ledwige et al., 1996). Therefore, in this paper, we wanted to systematically study the ability of the diclofenac anion to form ion-pairs with a variety of inorganic and organic cations. To promote the formation of ion-pairs, the aqueous solutions were prepared at increasing concentrations of chloride of the alkali metals or hydrochloride of the organic bases. The ion-pairs thus formed were continuously extracted from the aqueous solution by an immiscible organic phase. To achieve reliable results in this work we used an automated partition chamber previously employed, that guaranteed more precise measurements than the shaking flask method used for a preliminary study (Fini et al., 1993).

2. Experimental

2.1. Materials and methods

Sodium diclofenac was a commercial sample of analytical grade (Sigma Italia, Milano, Italy). Sodium (Na^+), lithium (Li^+), potassium (K^+), rubidium (Rb^+) and cesium (Cs^+) chlorides; diethylamine (DETA), diethanolamine (DEA), pyrrolidine (PY), *N*-(2-hydroxyethyl) pyrrolidine (HEPY), *N*-(2-hydroxyethyl) piperidine (HEPP) were commercial samples: when the bases were not analytical grade, they were distilled before use. Fig. 1 shows the structures of the organic bases in diagram form.

The desired concentration of the inorganic cation was obtained by introducing the selected chloride into the aqueous solution. The cation of the organic bases was directly prepared in aqueous solution, where a suitable amount of the selected base was neutralized by the addition of 1 M HCl solution up to the required final concentration (from 0.025 to 0.1 M). In order to buffer the solution at least at $pH = pK_a + 2$ of the selected base, a limited amount of the free base was also present.

2.2. Calculation of log P

Calculation of $\log P$ for the free bases was performed by means of the fragment method,

using the CLOGP Program version 3.4: the values together with the experimental ones are shown in Table 2.

Here the log *P* calculation for HEPY is reported (Fig. 1).

Hydroxy	−1.640
Tertiary amine	−2.180
Isolating carbons (6)	1.170
Hydrogen atoms (12)	2.724
Bonds (2 chains + 5 alicyclic bonds)	−0.690
Proximity effect (Y–C–C–X)	0.879
Calculated log *P*	0.263

2.3. Partition chamber

The scheme of the partition chamber, previously described (Rodriguez et al., 1989), is shown in Fig. 2. It consists of a thermostated Pyrex glass cell (length, 12.5 cm; inner diameter, 16 mm) closed at both ends with two cone-shaped bored Teflon stoppers, that allow the circulation of water phase.

The aqueous phase is circulated (flux 12.5 ml/min) through a spectrophotometric cell by means of an external peristaltic pump and dropped into the organic phase for the partition. In this way a large surface of the two phases is brought into interfacial contact and continuously removed. The process was followed until the equilibrium was achieved. The spectrophotometer (Philips PU 8720 UV/Vis) automatically records the absorbance values.

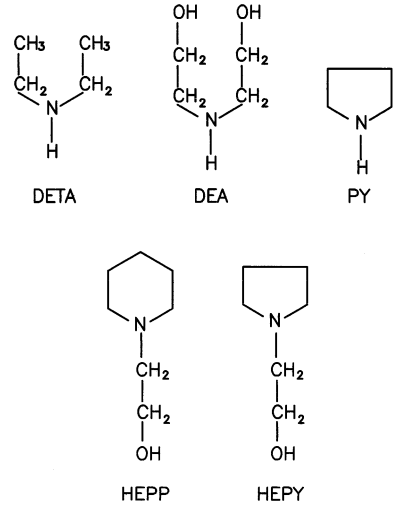

Fig. 1. Formulae of the organic bases showing the differences in terms of hydrophobic/hydrophilic contributions.

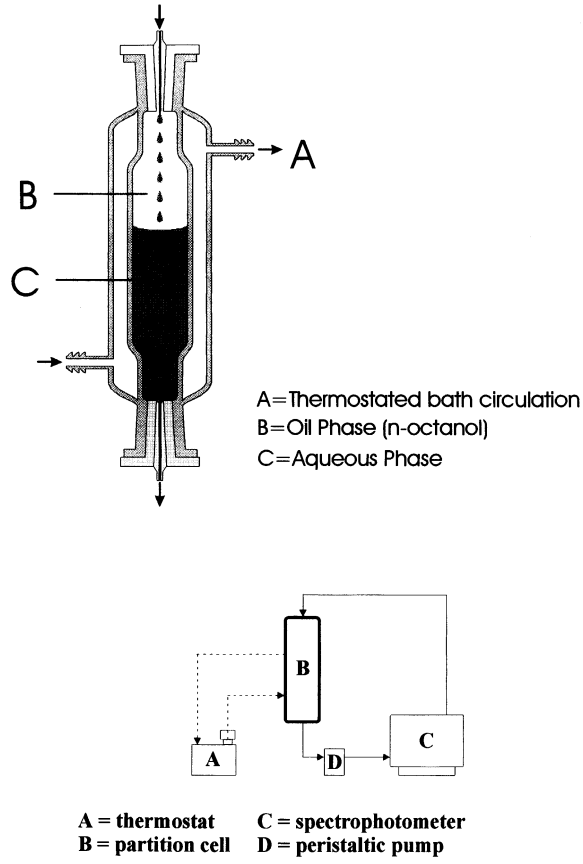

Fig. 2. Partition chamber.

The parameters used were: volume of the aqueous phase, 40 ml; volume of *n*-octanol, 3 ml; concentration of diclofenac anion, 10^{-4} M (as sodium diclofenac); concentration of cation, between 0.025 and 0.100 M; temperature, 37°C.

The profiles of the apparent partition coefficient, P', as a function of the concentration of the added cation, $[X^+]$, are shown in Fig. 3 for inorganic cations and in Fig. 4 for the organic cations.

3. Results and discussion

Many papers deal with the importance of the salt form with respect to the unionized form of a

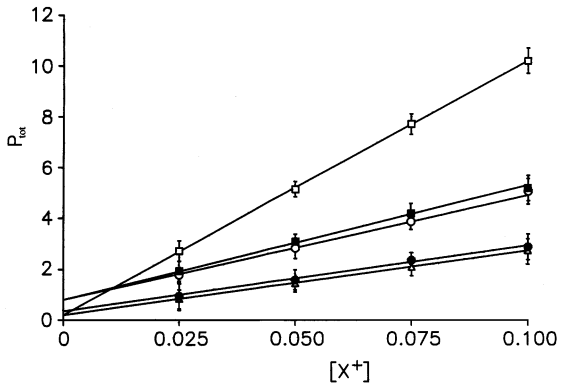

Fig. 3. Plot of the apparent partition, P_{tot} of diclofenac anion versus [X^+], the concentration of the inorganic cations in the aqueous phase.

drug (Berge et al., 1977): the major advantages of the salt form are related to the solubility (and dissolution rate), the melting point and stability. However, when the salt contains both an organic cation and anion, a residual degree of hydrophobicity could be present, despite the ionic character. It was reported, for instance, that salts of this type can be transported through hydrophobic membranes or display enhanced partition towards *n*-octanol (Hurwitz and Carney, 1978; Cools and Janssen, 1983; Yuko and Hiroshi, 1988; Falk, 1989).

Since the ability of the NSAID indomethacin to form ion-pairs with a few alkali metal cations was reported (Inagi et al., 1981), we studied the formation of ion-pairs in the case of the diclofenac anion coupled with a larger variety of inorganic and organic cations, to evaluate the parameters affecting this behaviour.

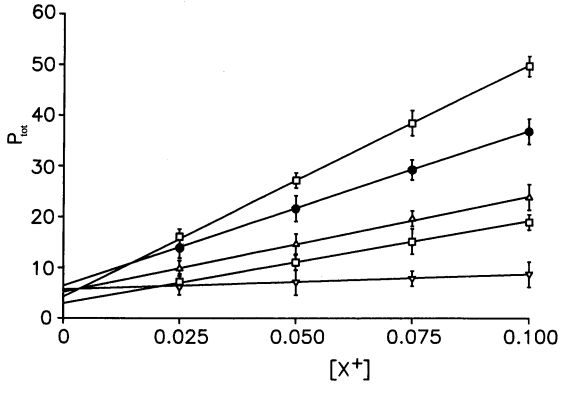

Fig. 4. Plot of the apparent partition, P_{tot}, of diclofenac anion versus [X^+], the concentration of the organic cations in the aqueous phase.

The molecule of diclofenac is the result of drug design (Sallmann, 1986): the project wanted to insert the best physical and chemical parameters in a single molecule (in terms of solubility, lipophilicity, molecular geometry, etc.) found for the known NSAID's up to 1970, in order to maximize the therapeutic effects and minimize the side effects. Because of its low aqueous solubility, diclofenac is mainly used as sodium or potassium salt, or as a salt with diethylamine (DETA) or *N*-(2-hydroxyethyl) pyrrolidine (HEPY) for topical formulations. This variety of chemical forms suggested checking the ability of these salts to form ion-pairs in solution and to extend the study to other structurally related diclofenac salts formed with organic bases.

The formation of ion-pairs in the case of diclofenac salts was previously suggested in different situations. The analysis of the crystal structure of the salt between diclofenac and some hydroxy bases reveals the presence of a complex network of hydrogen bonds between the anion and the cation, favouring ion-pairs (Castellari and Sabatino, 1994; Castellari and Ottani, 1995, 1996, 1997; Castellari and Sabatino, 1996). It was observed that when D/HEPY salt is dissolved at a constant concentration in different solvents, the electrical conductance of the solutions decreased with decreasing dielectric constant, attributed to increasing ion-association (Fini et al., 1994a). The formation of ion-pairs was studied in the case of sodium diclofenac (and other salt drugs), by conductance measurements (Lee et al., 1987). The formation was enhanced by decreased dielectric constant of the medium: ion-pair association constant was found practically zero in water, while it is 1115 in ethanol and 2969 in *i*-propanol.

The formation of an ion-pair was postulated in the case of sodium diclofenac to explain its permeation through a silicone membrane: the transport of the ionized drug becomes important when the release phase is non-aqueous and the dissolved salt could form ion-pairs in it.

To evaluate the formation of ion-pairs, we used the same technique previously reported (Inagi et al., 1981), that is the measurement of diclofenac anion partition towards *n*-octanol in the presence of increasing concentration of the cations in the aqueous phase.

The salts formed by the diclofenac anion (D^-) and each of the cations considered (X^+) are ionic in character and are soluble in water at the concentrations used. Their characterization in the solid state and the behaviour in solution are currently under study. In aqueous solutions the salts are dissociated and the equilibrium for the formation of an ion-pair ($X^+ \cdot D^-$):

$$X_w^+ + D_w^- \Leftrightarrow \{X^+ \cdot D^-\}_w$$

is shifted leftwards, because the association involves desolvation of the single ions, not very probable in this medium, especially at low concentrations. At increasing $[X^+]$ the equilibrium is shifted rightwards and the formation of the pair is improved; the presence of a second phase (*n*-octanol) appears important to show the association:

$$\{X^+ \cdot D^-\}_w \Leftrightarrow \{X^+ \cdot D^-\}_o$$

because the insoluble phase extracts the ion-pairs formed in water and allows their detection through the change of concentration by means of spectrophotometric measurement of the absorbance.

The formation constant of an ion-pair can be obtained by measuring an apparent partition coefficient of the absorbing species D^- at different concentrations of non-absorbing X^+ in the aqueous phase.

The difference in absorbance of the aqueous phase before and at the end of the extraction could be related to the transport of the absorbing species towards the oil phase:

$$P_{app} = \frac{[A_o - A_\infty]}{[A_\infty]}$$

According to the idea that the absorbing species could be present in the aqueous solution in different chemical forms, then in a system containing a weak acid (HD) and its salt with the cation X^+, the partition should concern the acidic form (HD), the ionized form (D^-) and eventually the ion-pair (X^+D^-): P_{app} actually represents a P_{tot}, as the sum of the contributions of each single species.

Therefore P_{tot} is defined as follows:

$$P_{tot} = \frac{\{[HD] + [D^-] + [X^+ \cdot D^-]\}_o}{\{[HD] + [D^-] + [X^+ \cdot D^-]\}_w}$$

Taking into account the expressions for the partition of each single species and the relationships which regulate their concentration as a function of $[X^+]$ and pH, and fixing suitable experimental conditions to exclude contributions to the partition of the species HD and D^-, a simplified equation (for details, see Inagi et al., 1981) can be obtained:

$$1/[X^+]_w = (K_{XD} \cdot P_{XD}) \cdot (1/P_{tot}) - K_{XD} \quad (1)$$

that contains two experimental parameters: the fixed concentration of the cation $[X^+]_w$ in the aqueous phase, added as chloride or hydrochloride; and the apparent partition coefficient P_{tot}. Plotting $1/[X^+]$ versus $1/P_{tot}$, in the presence of the ion-pair partition, a linear relationship should be obtained: K_{XD} can be determined as the ordinate intercept and P_{XD} from the slope (Inagi et al., 1981), where K_{XD} is the equilibrium constant for the formation of ion-pairs and P_{XD} is the partition coefficient of the ion-pair.

Further considerations are needed to exclude other phenomena different from the ion-pair partition. As suggested above, the apparent partition coefficient (P_{tot}) in the case of diclofenac salts can be the result of a variety of contributions: together with the partition of the unionized (HD) and ionized (D^-) form of diclofenac, also to be taken into account are the modification of the aqueous phase due to the presence of an excess of the free organic base, necessary to buffer the pH, and/or the salting out effect, due to increasing ionic strength in the aqueous phase.

The acidic diclofenac has a high $\log P$ value and a high molar extinction coefficient ($\log \varepsilon = 4.0$): it was important, therefore, to keep the pH under control to avoid its contribution to the partition process of the ion-pair. In the case of organic cations the aqueous solution was buffered, partially neutralizing the corresponding base with concentrated HCl, leaving in each case

Table 1
Parameters for the ion-pair formation between diclofenac and inorganic cations

Inorganic cation	Hydration enthalpy, $-\Delta H$ (kJ mol^{-1})	Ionic radius (pm)	P_o (± 0.1)	K_{XD} (± 0.8)	P_{XD} (± 2)	E_{XD} (± 5)
Li^+	543	60	0.2	2.5	64	160
Na^+	433	95	0.8	9.6	12	115
K^+	349	133	0.7	8.0	10	80
Rb^+	324	148	0.3	7.0	7	49
Cs^+	291	169	0.2	6.2	6	36

an excess of free base, enough to fix the pH at least to 8.0. Since diclofenac has a $pK_a = 3.80$, at this pH the concentration of the free acid is less than 0.01% and the contribution of this species can be considered negligible.

Moreover the possibility could also be considered that, as a consequence of a hydrolysis reaction ($D^- + H_2O \Leftrightarrow HD + OH^-$), acidic diclofenac (HD) could be formed and continuously extracted by the *n*-octanol. If this were true, no difference would have been found among all the cations examined, since in each case the species partitioned would have always been the same; while, on the contrary, the behaviour changes as different cations are considered.

The influence of the free base on the partition (all the bases considered for the salt formation are freely soluble in water) was evaluated for the DEA cation: in this case the highest concentration of the free base (0.0121 M) was used to buffer the system at the highest [X^+] studied. Fig. 4 shows that practically no difference of P_{tot} was observed in the whole range of [X^+] examined.

The contribution to partition of the free diclofenac anion (D^-) was calculated and that of a salting out effect was considered in the case of D/Cs salt.

Fig. 3 shows the plots $1/[X^+]$ versus $1/P_{tot}$ and Table 1 summarizes the parameters for the ion-pair formation (K_{XD} and P_{XD}) in the case of alkali metal cations, obtained by fitting the experimental data by means of the Eq. (1).

The plots are linear with an ordinate intercept P_o positive, even though low: this value can be considered the apparent partition coefficient of the salt XD. This value is comprehensive of the contributions to partition of all the species present in the solution and phenomena different to the ion-pair partition. The low P_o value found for Cs^+ and the small changes in P_{tot} found at increasing [Cs^+] suggest that Cs^+ ion does not allow the formation of an ion-pair with diclofenac anion: therefore the small changes of P_{tot} observed with increasing [Cs^+] can be attributed only to a salting out effect. As a consequence, taking into account: (a) the highest value found for P_o of all the cations studied; (b) the calculated value of log *P* for the diclofenac anion; (c) the small contribution of the salting out effect, it can be concluded that, when the P_{tot} values are found to be at least higher than 3, the change in P_{tot} can be confidently attributed to the ion-pair partition.

3.1. Inorganic cations

Most P_{tot} values obtained when X^+ is an inorganic cation are low and change very little with [X^+], indicating that inorganic cations have a weak ability to promote partition of the diclofenac anion, even at high [X^+] values.

Two parameters play opposite roles in the formation and partition of ion-pairs in the case of inorganic cations: the ionic radius and the desolvation enthalpy of the cations. Ions with a small radius can approach the anion more closely; however, high desolvation energy hinders the pairing. While for other alkali cations the two parameters almost balance each other, in the case of Li^+, the required relatively high desolvation enthalpy (Table 1) makes the D/Li association (low K_{XD}) unfavourable. However the high ionic density on the small Li^+ ion creates an intense electrostatic field and improves the coulombic interactions in the formation of the ion-pair should that result

tightly close. This fact efficiently masks the ionic charges and makes the ion-pair more hydrophobic (high P_{XD}), of the same order of magnitude of the organic pairs (Table 2), with a high extraction constant (E_{XD}).

Hydration is dependent on the ionic radius of the species present in the solution: the alkali metal cation and the large organic anion. Table 1 shows that a large enthalpy of hydration is associated with the cations (Rubino, 1989). Since we considered a series of salts where the structure of the anion is constant, the contribution associated to its size and desolvation energy shall be constant to the whole process. Moreover it was suggested that the diclofenac anion is not hydrated in water (Maitani et al., 1993). In fact, its size, as determined by an atomic or group contribution method (422 pm) (Lee et al., 1987), or as determined for the molar volume of diclofenac (473 pm), is almost the same as that determined by the conductivity method (427 pm) (Maitani et al., 1993). This result is justified by the large hydrophobic portions present on the molecular structure of diclofenac, that do not favour interactions with the aqueous environment and also account for the association of diclofenate anions in micelle-like aggregates (Fini et al., 1991, 1994b). In this case, this aspect supports partition of the overall ion-pair and allows a rather general conclusion that the salt between a large hydrophobic drug with common alkali metal ions (e.g. Na^+) can promote unforeseen and interesting behaviour to the absorption of the active principle (Roda et al., 1990).

Except for the case of Li^+, P_{XD} values for inorganic cations are comparable; in the case of Na^+ and K^+ these values are also comparable to those found in the case of ion-pair with indomethacin with these two ions (Inagi et al., 1981).

The behaviour of Li^+ is very interesting: this ion promotes the partition of the diclofenac anion to the highest level because the ion-pair formed displays the highest partition coefficient. The result can explain the in vivo increased clearance of Li^+ ions during the administration of diclofenac: the ability of diclofenac to selectively interact with Li^+ ions slows down the excretion and raises the plasma concentration of alkali cation originating side effects (Reimann and Frolich, 1981; Danion et al., 1987); it also confirms the previous report that a concomitant therapy with diclofenac and lithium should be approached with caution (Miller and Prichard, 1990) because of their significant interaction (Davies and Anderson, 1997).

3.2. Organic cations

In a simplified diagram form, Fig. 1 shows the molecular structure of the bases employed to prepare each salt. It can be observed that in the selected group of the bases (X) different, but well defined, hydrophilic or hydrophobic contributions have been considered, starting from DETA, as a reference. These differences concern the presence of hydroxy groups or the closing of the chain into a ring. Table 2 shows the log P value for the free bases, either experimental or calculated with the fragment method. In the case of DETA, HEPP and DEA, the two sets of values practically are the same. For HEPY no experimental value was found in the literature and, therefore, only the calculated value was consid-

Table 2
Parameters for the ion-pair formation between diclofenac anion and organic cations

Organic cation	Log P (free base)	P_o[a] (± 0.1)	K_{XD}[a] (± 2)	P_{XD}[a] (± 0.5)	E_{XD}[a] (± 20)
DETA	0.58/0.540[a]	4.3	4	150	600
DEA	−1.43/−1.436	5.7	42	10.9	458
PY	0.46/−0.004	3.1	9	38.0	342
HEPY	−/0.263	5.3	14	40.7	570
HEPP	0.96/0.822	6.7	10	70.2	702

[a] Experimental/calculated.

ered. In the case of PY, experimental and calculated values notably differ. Probably the calculation is not able to take into due account the changes introduced into the molecule by the formation of a ring (see below) (Hansch and Leo, 1979).

Also in the case of organic cations, increasing $[X^+]$ improves the partition of the diclofenac anion towards the *n*-octanol: the slopes of the plots in Fig. 4 are higher than those observed for alkali metal cations, indicating a major ability of the organic cations to originate species more relative to the lipid phase. This was somehow expected according to the fact that in this group of salts both anion and cation are organic. The P_{XD} values (Table 2) are in the sequence: DETA > HEPP > HEPY ≅ PY > DEA. DEA cation in particular behaves like an inorganic cation as far as P_{XD} is concerned. The two hydroxy groups at the end of the ethyl chains (Fig. 1) make the DEA cation the most hydrophilic one of the group, especially compared to the DETA one. The coupling of diclofenac anion with this last cation ensures the highest slope (Fig. 4).

Comparison between DETA and PY shows the increase of hydrophilicity as a consequence of the ring formation. The same occurs in the oxygen analogue couple, diethyl ether and tetrahydrofuran: while the first solvent has a limited solubility in water, the second one is soluble in all the ratios. To explain this difference, James (1986) suggested a steric reason: the ring blocks the two covalent bonds attached to the oxygen, thus improving the exposure of unshared electrons on the oxygen atom to the solvating medium.

The pairs made by HEPY and PY have practically the same P_{XD}; the effect of the hydroxyethyl moiety cannot be properly evaluated due to the difference between the calculated and experimental log *P* for PY.

HEPY and HEPP differ only in the size of the ring. The P_{tot} values proved to be very sensitive to the hydrophobicity difference (Hansch and Leo, 1979), related to the presence of an additional $-CH_2-$ group in HEPP (Figs. 1 and 4). These two cations are also described as forming an ion-pair with the diclofenac anion in the solid state Castellari and Sabatino, 1994, 1996); if we assume that this interaction operates to some extent to promote the ion-pair formation also in aqueous solution, their relatively high P_{tot} values are not, therefore, surprising, compared to PY.

While the P_{XD} values are higher for the organic than for inorganic cations, the values of K_{XD}, almost comparable in both cases, suggest that in aqueous phase the concentration of ion-pairs is very low in each case.

The highest formation constant K_{XD} was found for the DEA cation; this seems to suggest a possible role of the hydrogen bonds in the formation of ion-pairs. The salt D/DEA was described in the solid state as a sort of a 'supramolecule' (probably existing also in solution), the interaction between the anion and the cation being very strong (Castellari and Ottani, 1995). However, due to the low value of the slope for this pair (Fig. 4), the weight of the experimental error makes K_{XD} and P_{XD} for D/DEA little reliable. Taking into account that in aqueous medium solute/solvent interactions, and thus solvation, are dominant over cation/anion interactions, eventual hydrogen bonds can become operative when the equilibrium of formation is shifted rightwards for the presence of the continuously extracting phase. In this connection, also the differences, even though small, in the case of K_{XD} values observed for HEPY and HEPP can be significant and originated by the same mechanism: in fact these two bases differ from DETA and PY by the presence of a hydroxy group; moreover, the tendency to also form ion-pairs is documented in the solid state for this couple of salts, as observed above (Castellari and Sabatino, 1994, 1996).

A third parameter can be obtained from K_{XD} and P_{XD}, namely $E_{XD} = K_{XD} \cdot P_{XD}$, defined as 'extraction constant'. E_{XD} can be easily referred to the equilibrium:

$$D_w^- + X_w^- \Leftrightarrow \{X^+ \cdot D^-\}_o$$

which describes the 'extractability' (Inagi et al., 1981) of the ion-pairs, that is the ability of a lipid phase to promote the ion-pair formation in the aqueous phase, by shifting the equilibrium rightwards and extracting the final product.

From Tables 1 and 2 it emerges that diclofenac ion-pairs made with organic cations have higher E_{XD}, suggesting their importance in driving the formation of species, which conjugate an ionic (hydrophilic) character together with the (hydrophobic) affinity towards a lipid phase. Since D^- is constant in these ion-pairs, differences should be attributed to the cations. When E_{XD} values are plotted versus the log P of the free bases a linear relationship between these two parameters can be observed. Caution should be used in assuming that the sequence of the log P for the cations (X^+) in the ion-pairs is the same as that for the free bases; the linear relationship, however, should indicate that the driving force for the partition of the ion-pairs of these diclofenac salts is primarily related to the hydrophobicity of the cation (an ion-association complex between diclofenac anion and methylene blue is easily extracted by chloroform) (Sastry et al., 1989).

A few of the consequences of these results can be as follows:

- Due to the variety of the salting agents, the chemical form of a salt represents an interesting alternative for a drug with respect to the unionized form, not only in terms of solubility or dissolution rate, but also of partition.
- Drugs in the form of salts maintain a finite ability to partition, provided that anion and cation are able to couple as ion-pairs. An important role is played by the nature of the counter ions: (a) organic counter ions behave better than inorganic ones; (b) hydrophobicity of the organic counter ions improves the partition coefficient (P_{XD}) of the ion-pairs; (c) the possibility to form hydrogen bonds, even though not clearly demonstrated in solution, between anion and cation, represents additional assistance in forming the ion-pair and increases the formation constant (K_{XD}).
- In the form of an ion-pair a drug maintains its properties towards partition if this form is not altered by media with adverse pH. This circumstance can be encountered in the use of these salts as topical formulations. The chemical form, soluble in water, allows a hydrophilic pharmaceutical form, such as a gel. The transdermal route of administration prevents the destruction of the chemical form, the pH changes being slow and limited, before its dermal absorption. The formation of ion-pairs can play a positive role in the absorption of the drug deposited on the layer of the skin, that extracts the active agent in the form of ion-pair and transports it through the hydrophobic domains of the horny layer.

The absorption of the active agent from a commercial topical formulation, containing diclofenac in the form of DETA or HEPY salt, such as gel or plaster, is reported (Riess et al., 1986; Assandri et al., 1993). Among the commercial salts, D/HEPY appears to form tighter ion-pairs and this agrees with and explains the high solubility measured in non-polar solvents; while the salt D/DETA compensates for a lower association constant with a higher partition coefficient of the ion-pair. The ability of both cations to 'extract' the diclofenac anion is comparable, as is shown by the E_{XD} values. Finally, the presence of a salt form in topical formulation suggests the possibility of enhancing the absorption by means of iontophoresis: in the case of ion-pairs the absorption can occur either via passive diffusion across the lipid matrix of the horny layer of the skin or through hydrophilic pores present in the skin (Nakhare et al., 1994; Varghese and Khar, 1996). Salt drugs, with the ability to dissociate and to form ion-pairs offer a better chance for absorption, with the possibility of alternative pathways and absorption mechanisms.

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