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Solubility and solubilization properties of non-steroidal anti-inflammatory drugs

Adamo Fini*, Giuseppe Fazio, Giorgio Feroci

Istituto di Scienze Chimiche, Facoltà di Farmacia, Via S. Donato 15, I-40127 Bologna, Italy

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Abstract

Ten non-steroidal anti-inflammatory drugs (NSAID) of the acetic and propionic classes were analyzed in the form of salts to disclose the solubilization property of their aqueous solutions toward a lipid probe (the azo-dye Orange OT). This property is related to the self-aggregation of the anions above a concentration value that differs for each drug: indomethacin and fenclofenac showed solubilization ability in the form of sodium salts in pure water (starting from 30 and 40 mM, respectively); these values decreased with increasing ionic strength. In the case of diclofenac it was necessary to use a salt prepared with an organic base, that displayed a solubility higher than that of the sodium salt, required to overcome the critical value (35 mM). Naproxen, sulindac, ketoprofen, indoprofen were used at high concentrations of their sodium salts (100–160 mM) and solubilize the dye in the presence of a high total ionic strength. Alclofenac did not display solubilization ability; fenbufen and ibuprofen were tested as salts of an organic base: results were not conclusive because the presence of the organic base in the salt form and in the solution, as added electrolyte for the ionic strength, affected the results of the solubilization tests. The results are briefly discussed in terms of hydrophilic/hydrophobic balance present on the anion of the NSAID examined, as evaluated by the fragment constant approach.

Keywords: Anti-inflammatory drugs; Critical micellar concentration; Solubility and solubilization; Ionic strength; Fragment constant; Hydrophilic/hydrophobic balance

1. Introduction

Surface activity and the related properties are not unique to soap and detergent solutions: many drugs are also surface active at the air-solution interface and can self-aggregate forming micelles or micelle-like structures above a critical concentration value (Florence and Attwood, 1982; Attwood and Florence, 1983).

While many types of drugs, such as antihistamines, anticholinergics, antidepressants and tranquillizers (Attwood and Florence, 1983), phenothiazines and many others (Attwood et al., 1974), have been listed among surfactant systems and the consequence of this behaviour has been widely and critically discussed, little information is available for non-steroidal anti-inflammatory drugs (NSAIDs).

* Corresponding author. Tel: + 39 51 244540; Fax: + 39 51 249770.

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The ability of indomethacin to interact with bile salts was previously reported (Miyazaki et al., 1979b, 1981b), possibly through the formation of mixed micelles; there was also some evidence that sodium salicylate associates in solution at concentrations greater than 20% w/v, solubilizing diazepam (El-Khordagui et al., 1980) and decreasing the surface tension of water (Saleh et al., 1980). A recent paper reported also the liquid crystalline properties of the aqueous solutions of some diclofenac salts (Kriwet and Müller-Goymann, 1993).

Since many surface activity events occur above a fixed concentration, in many cases this activity cannot be observed for other NSAIDs due to the limited solubility of the chemical form employed. This was found in the case of diclofenac (Fini et al., 1991) and can be encountered, for instance, within some bile acids (lithocholic acid): when the compounds are very poorly soluble in their acidic form, the sodium salt form (the most frequently used salt form for these drugs) in some cases has a limited solubility, lower than that necessary to witness solubilization.

In this work we studied the surfactant behaviour of ten NSAID solutions: the NSAIDs were chosen within the acetic acid and propionic acid classes and were used in the form of sodium salts or, in the case of low solubility of this salt form, as salts with a hydrophilic organic base. Among the many physical and chemical properties generated in solution by a surface active structure, the most interesting one is micellization, i.e. the formation in solution of aggregates capable of solubilizing hydrophobic materials of limited water solubility. Solubilization occurs in a micelle-rich solution and the concentration at which it starts to be measured is recorded as the critical micellar concentration (CMC) of the compound under examination. Solubilization of an azo-dye probe was therefore chosen as a simple initial approach to study the self-aggregation of NSAIDs, among a variety of possible physical and chemical parameters (Fini et al., 1993a).

The experimental results are reported in terms of the lowest concentration necessary to start solubilization and the values are briefly discussed in terms of compound structures, using the fragment constant approach (Hansch and Leo, 1979).

2. Experimental section

2.1. Materials and methods

Alclofenac (ALCL) (L.T.B., Bruxelles, Belgium), Diclofenac (D) and its HEP salt (D/HEP, m.p. 102–104°C)) (IBSA, Lugano, Switzerland), Indomethacin (INDOMET) (Farmaceutici Chiesi, Parma, Italy), Naproxen (NAP) (Alfa-Wasserman, Bologna, Italy) were gifts of the manufacturers. Fenclofenac (FENCL), Ibuprofen (IBU) Indoprofen (INDOPR), Ketoprofen (KET), Fenbufen (FENB) and Sulindac (SUL) were commercial samples (Sigma Aldrich, Milan, Italy): all the NSAIDs were of pharmaceutical grade and used as received. Some physical chemical parameters for these compounds are listed in Table 1.

N-(2-hydroxyethyl) pyrrolidine (HEP) was a commercial sample (Fluka, Buchs, Switzerland): it is freely soluble in water and was freshly distilled prior to use ($K_p = 75$°C/14 mmHg). Aqueous solutions containing HEP hydrochloride were prepared up to 0.5 M by direct neutralization of the base in water, adding an equivalent amount of 1 M hydrochloric acid solution and potentiometrically adjusting the pH to 7.50. NaCl was analytical grade (Carlo Erba, Milan, Italy).

Orange OT is a commercial azo-dye (Sigma Aldrich), with a maximum peak at 492 nm (log ε: 4.12, Hitachi 220S UV/VIS): in the presence of some NSAID salt a slight shift of the maximum towards 495 nm was observed.

The NSAID salts were prepared mixing in water equivalent amounts of the acids and the appropriate base; all the work solutions were prepared by dilution: when necessary pH was appropriately adjusted to the value 7.50.

2.2. Solubility measurements

2.2.1. Salts

Five milliliters of bidistilled water were prepared containing increasing NaCl concentrations (0.5–1.0–1.5–2.0 M): weighted amounts of the sodium salt of all the NSAIDs were added until

Table 1
Chemical-physical properties of NSAIDs

	MM[a]	m.p.[b] (°C)	pK_a	λ[c] (nm)	Logε[d]	Solubility[e]	
						H (μM)*	Na (mM)**
Alclofenac	226.66	92–93	4.90	279	3.28	750	4
Diclofenac	296.13	155–156	3.80	276	3.93	8	6
Fenclofenac	297.13	134–136	4.35	276	3.20	140	3
Indometacin	357.81	155/162	4.50	226	4.52	<0.1	110
Sulindac	356.42	182–185	4.70	286	4.20	10	720
Fenbufen	254.29	185–187	4.50	285	4.38	5	1.5
Ibuprofen	206.27	75–77	4.55	264	2.76	380	185
Indoprofen	281.32	213–214	4.60	276	4.17	15	17
Ketoprofen	254.20	94–95	4.60	260	4.20	700	21
Naproxen	230.26	155–156	4.60	271	3.71	70	350

[a]Molecular mass; [b]melting point of the acids; [c]analytical wavelength; [d]logarithm of the molar extinction; [e]solubility of the protonated acid in 10^{-2}M HCl* and of the sodium salt in 0.5 M NaCl**.

saturation was achieved at 25°C and stored at this temperature for a week. The concentration of each drug was spectrophotometrically determined at the wavelength reported in Table 1, after careful filtration (0.2 μm) and suitable dilution. The solubility values were confirmed after a further week, because many salts tend to form supersaturated solutions, that only very slowly reach equilibrium.

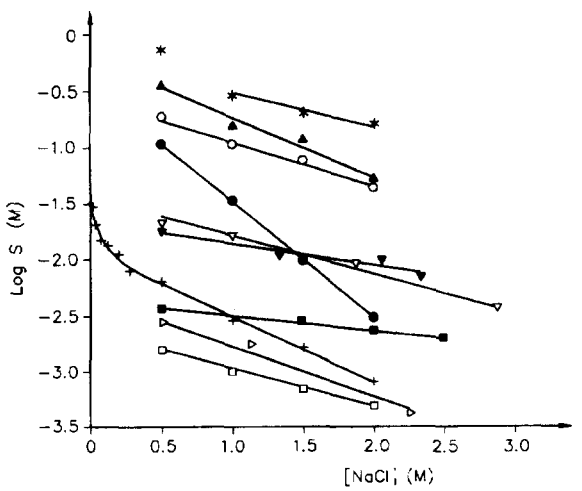

Fig. 1. Logarithm of the molar solubility of sodium salt NSAID as a function of the added NaCl concentration: *, sulindac; ▲, naproxen; ○, ibuprofen; ●, indomethacin; ▽, ketoprofen; ▼, indoprofen; +, diclofenac; ■, alclofenac; ▷, fenclofenac; □, fenbufen.

Fig. 1 shows the relationship between the logarithm of solubility versus the concentration of the added electrolyte. The solubility values reported in Table 1 are those determined in the presence of 0.5 M NaCl.

2.2.2. Acids

A small amount of each NSAID, in the acidic form, was added to 10 ml of 10^{-3} M HCl aqueous solution: the final pH was adjusted to the value 3.0. The systems were kept at room temperature for 1 month, under occasional shaking. The concentrations were spectrophotometrically read and the solubility values are shown in Table 1.

2.3. Solubilization study

In a preliminary test three aqueous solutions of each NSAID sodium salt were prepared at concentrations of 50, 100 and 200 mM (when possible); a few crystals of Orange OT were added and the samples were shaken for 24 h; when these levels of concentration were not achieved with the sodium salt, we used the HEP salt; when solubilization was not observed in pure water, a common ion electrolyte was added up to 0.5 M.

The solubilization of the dye was then systematically examined in the optimum range of concentration for each salt, from 10 to 300 mM, using the appropriate salt form and ionic strength:

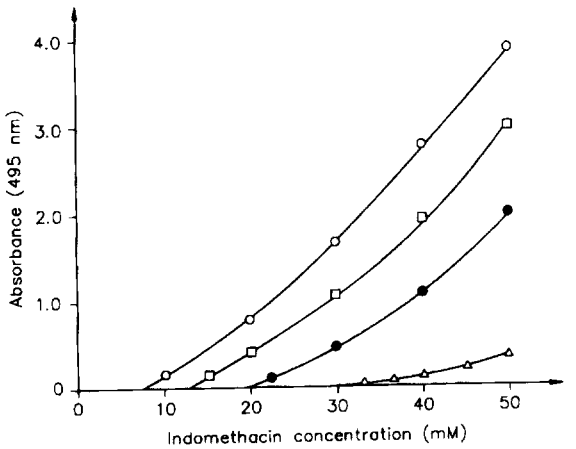

Fig. 2. Solubilization plot of Orange OT in solution containing sodium indomethacin in the presence of added NaCl: ▷, no NaCl added; ●, up to 0.15 M; ●, up to 0.30 M; ○, up to 0.50 M total Na^+.

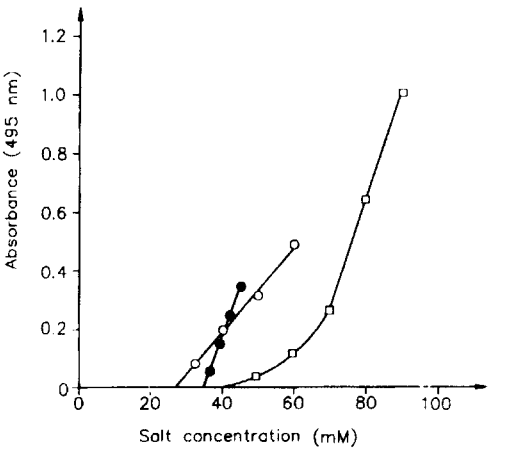

Fig. 3. Solubilization plot of Orange OT in solutions containing sodium indomethacin (○), HEP diclofenac, (●) and sodium fenclofenac (□) in water.

in pure water for D/HEP; at increasing (0–0.5 M, INDOMET/Na and FENCL/Na) or at fixed (0.5 M) total ionic strength, by addition of NaCl, for other NSAIDs as sodium salts; IBU and FENB were used as HEP salts and the total ionic strength was fixed using HEP.HCl.

Ten vials containing each NSAID salt at progressively increasing concentration were supplemented with a few crystals of Orange OT. In some cases the ionic strength was adjusted up to a total value 0.5 M, including the NSAID salt and the electrolyte. The mixtures were stirred for 2 days and then filtered. The absorbance of the solutions was read at 495 nm, against reference samples containing the NSAID salt and the electrolyte at the same concentration. The solubilization diagrams were drawn plotting absorbance versus concentration values (Fig. 2, Fig. 3 and Fig. 4); extrapolation to zero absorbance gives the lowest concentration necessary for solubilization, reported in Table 3 and Fig. 2, Fig. 3 and Fig. 4: Fig. 2 shows the influence of the ionic strength on the CMC values for INDOMET/Na; Fig. 3 shows the solubilization plot of the salts INDOMET/Na, FENCl/Na and D/HEP in water; Fig. 4 shows the solubilization of the remaining NSAID sodium salts at 0.5 M total ionic strength (NaCl).

Throughout this work the term critical micellar concentration (CMC) was used, according to its current use for surfactants, even though in the present system it is not known whether the aggregation is critical or micelles are really formed as in the case of classical long-chain surfactants.

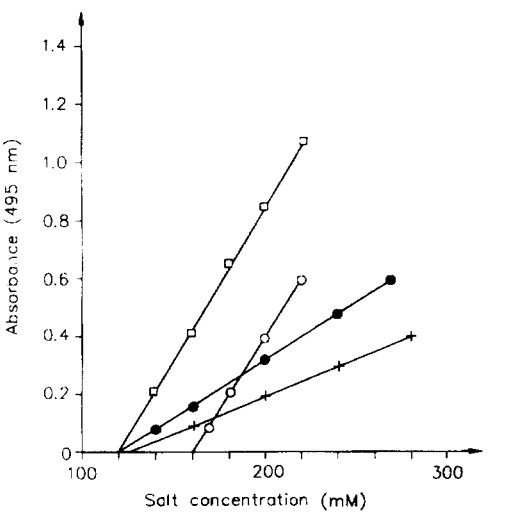

Fig. 4. Solubilization plot of Orange OT in solutions containing: indoprofen (□), sulindac (●), ketoprofen (○) and naproxen (+) as sodium salts in the presence of NaCl added up to 0.5 M total Na^+.

Table 2
Calculated log P for diclofenac

Fragment: –COOH (×1)		−1.03
Fragment: –NH– (×1)		−0.09
Fragment: –Cl (×2)		1.88
Aliphatic isolating carbon		0.195
Aromatic isolating carbon (×12)		1.56
Hydrogens on isolating carbons (×9)		2.04
Factor: chain (×2)		−0.24
Factor: electronic interaction		0.45
	C Log P	4.77
	Log P*	4.40

2.4. Calculation of log P

Calculation of the log P values for each NSAID was performed by means of the fragment method (Hansch and Leo, 1979) and using the CLOGP Program, version 3.4 (Pomona College MEDCHEM Program, 1986). The program calculates the Log P values as a summatory of each hydrophilic (negative) and hydrophobic (positive) contribution of the structural terms. As an example Table 2 shows the output of the program for diclofenac acid.

The log P of the anions was calculated from that of the acids subtracting the contribute of the carboxyl group (fragment constant for –COOH: −1.03) and adding that of the carboxylate (fragment constant for $-COO^-$: −5.19). In order to calculate the hydrophilic/hydrophobic ratio (HHR) of the anions, we attributed the main hydrophilic contribution to the carboxylate group and the hydrophobic weight to the remaining part of the molecule. The ratios (HHR) between these values are reported in Table 3 as absolute values, together with other parameters.

3. Results and discussion

3.1. Solubility study

Previous thermodynamic and kinetic examination of the behaviour in aqueous solution of the listed NSAIDs reported a dominant hydrophobicity of these compounds, that have weak acidity, low solubility and dissolution rate in water, but high partition coefficient, in their acidic form (Fini et al., 1984, 1985, 1986, 1988; Zecchi et al., 1984). The sodium salts were more soluble in water than the corresponding acid form (Table 1), as expected, but in some cases not soluble enough for the current study. Following the results obtained in a parallel study on the solubility of diclofenac salts (Fini et al., 1991), we chose the organic base *N*-(2-hydroxyethyl) pyrrolidine (HEP) as an alternative base to sodium hydroxide for the salt formation. In the case of diclofenac, HEP improved the solubility and the delivery rate from monoliths (Fini et al., 1992).

The addition of a freely soluble electrolyte usually reduces the solubility of a poorly soluble salt, having a common ion (Miyazaki et al., 1979a, 1980, 1981a), because the ionic product can be exceeded; moreover also the reduction of solubility by a salting out effect due to the increasing ionic strength, must be considered. Fig. 1 shows that the logarithm of the molar solubility of the NSAID sodium salts is inversely related to the concentration of the added electrolyte (NaCl), as suggested by the empirical Setschenow equation. This equation, that describes the salt effect on the solubility of non-electrolytes, was found to hold for the NSAID salts of this study from concentration of NaCl 0.5 up to more than 2 M. In this

Table 3
Experimental and calculated log P, hydrophilic/hydrophobic ratio (HHR) and lower limit concentration (mM) for the solubilization (s.c.) of Orange OT in aqueous solution of NSAID as anion

NSAID	log P		HHR	s.c.
	calc.	exptl		(mM)
Alclofenac	2.42	2.48	1.50	–[a]
Diclofenac	4.77	4.40	0.89	36[b]
Fenclofenac	4.87	4.80	0.88	40[b]
Indomethacin	4.23	4.27	0.99	27[b]
Sulindac	2.76	3.02	1.40	12[c]
Fenbufen	3.11	3.15	1.25	–
Ibuprofen	3.83	3.50	1.07	–[a]
Indoprofen	2.74	2.77	1.37	120[c]
Ketoprofen	2.79	3.12	1.36	160[c]
Naproxen	2.82	3.18	1.34	120[c]

[a]See text; [b]in water; [c]in the presence of 0.5 M total Na^+.

range both the adverse salting out effect and the overcoming of the solubility product tend to lower solubility: these two effects operate with different weight and the relationship between log S and [NaCl] is fairly linear. For soluble NSAID salts and at NaCl concentration lower than 0.5 M the relationship is no longer linear due to the onset of a different mechanism (first steps of the self-aggregation?) and the extrapolation to zero NaCl concentration therefore produces incorrect solubility values, different from those directly determined in pure water (when possible): this is shown in Fig. 1 only for the sodium diclofenac, but the difference was found to be even higher for some other compounds. This aspect is very important to our purposes: in fact while in the solubility studies 0.5 M is referred to the $[Na^+]$ added as NaCl, in the solubilization study that value represents the total $[Na^+]$ from the NSAID sodium salt and from NaCl, added to adjust the ionic strength to a common value. Therefore at the highest ionic strength (0.5 M) used for solubilization study, the solubility was lower than the concentration necessary for the onset of solubilization only in the cases of sodium salt of D, FENB and IBU: for the sodium salt of these compounds the solubility is decreased by the presence of NaCl to such a level that it could no longer be possible to achieve the possible micellar range; in these cases solubilization was examined employing the more soluble HEP salt and in the absence of added an electrolyte (D) or in the presence of a suitable electrolyte (IBU, FENB); in other cases NSAIDs were tested as sodium salts

3.2. Solubilization study

The ten NSAIDs examined can be divided into three groups, as far the solubilization of Orange OT is concerned.

The first group contains alclofenac, that did not show solubilization ability, at low or high ionic strength, in the form of sodium or HEP salt, in solutions up to 0.2 M.

The second group comprises NSAID salts able to solubilize Orange OT in pure water: indomethacin, fenclofenac, diclofenac. INDOMET/NA displays solubilization of the dye in water starting from 30 mM (about 1.1 g%). Fig. 2 shows the solubilization plot of INDOMET/Na at increasing NaCl concentrations: CMC decreases when ionic strength increases. This is a typical phenomenon related to self-association, observed in the case of many surfactants. Moreover, as ionic strength increases, the aggregates can increases in size thus enhancing the extent of solubilization, as indicated by the slopes of the linear portion of the curves. The optical density of the solutions is not linear with the concentration of the salt: CMC was evaluated linearly extrapolating the final portion of the curves.

The influence of the counter-ion on solubilization was examined using sodium or HEP indomethacin salts. Slight differences were observed for the CMC and the slope of the solubilization plot in water; in the presence of 0.15 M added electrolyte made by NaCl or HEP.HCl, differences concerning both values were observed. This suggests that the presence of the electrolyte containing the large organic cation plays some, as yet undefined, role in the solubilization of the dye and alters the final results.

The solubilization plot obtained in the case of FENCL/Na is linear only well above the CMC: according to the extrapolation of the linear ascending portion, CMC is 60 mM; following the profile of the starting portion of the plot, that shows a fair curvature, the value of 40 mM could be estimated. This appears to be a general case: see Fig. 2 for INDOMET/Na.

Diclofenac also solubilized the dye at low concentration (36 mM), but this value, due to the lower solubility of the sodium salt (30 mM), could be reached using the HEP salt: however, since this salt also has limited solubility (46 mM), solubilization was followed in a small range of concentrations and in the absence of added electrolyte. The behaviour in solution of these three compounds can be considered closest to that of common surfactants, mainly for the relatively low CMC value (Fig. 3).

The third group contains NSAIDs that solubilize the azo-dye only in the presence of high total ionic strength. Two of them have solubility problems (Fig. 1): FENB/Na has a limited solubility; IBU/Na has a higher solubility, but the micellar

level could not be reached in pure water. In both cases the use of the HEP salt and the presence of 0.5 M HEP.HCl led to solubilization of Orange OT. Since the results must be considered with caution, in line with previous observations concerning INDOMET/HEP, we shall not discuss these results further.

Other NSAID salts overcome the critical value only at high concentrations and to compare results we carried out the experiments at 0.5 M total ionic strength, a value that included all the different concentration ranges examined. The critical solubilization concentrations are found above 100 mM (Fig. 4), much higher than for common surfactants . These concentrations were found in the presence of much higher ionic strength than usual: for the sodium bile salt the values are between 5 and 15 mM (in 0.15 M NaCl). This can be attributed to the structure of the molecules of NSAID: when compared with common surfactants the hydrophobic region present in the NSAID molecules is small. Replacement of the flexible hydrophobic moiety of the alkyl fatty acids with a rigid aromatic or heterocyclic ring system can have very pronounced effects on the way and extent in which the molecules are arranged within the aggregates, so much so that the process of association may be regarded as a stacking process rather than a micellization (Mukerjee, 1974), even though the term critical micellar concentration is used.

We evaluated the hydrophilic/hydrophobic balance (HHB) present on the molecules using the fragment constant approach (Hansch and Leo, 1979). This method allows separate evaluations of the contributions of the hydrophilic and hydrophobic portions of a molecule to the overall hydrophilic/hydrophobic balance and to make the calculation easier, we neglected the contribution of the cation. We attributed the main hydrophilic contribution to the carboxylate group of the NSAID anion and calculated, as appropriate, the contributions of all other groups and factors present in the different NSAID anions. The ratio between these two values was used to evaluate the hydrophilic/hydrophobic balance (HHB) present on the anions: the values obtained suggest a dominant hydrophilicity for most anions, but with different weight; they define three ranges : 0.5–1, 1–1.5, >1.5. In the first range we found molecules with the lowest CMC values, that can self-aggregate in pure water and in the absence of ionic strength: indomethacin, diclofenac, fenclofenac. In these anions the hydrophobic contributions overcome that of carboxylate; ibuprofen also falls into this range, but it shows solubility problems as a sodium salt. More hydrophilic anions behave in solution as free electrolytes at low concentrations and ionic strength: this was found to be the case for indoprofen, ketoprofen, naproxen, sulindac. The anions of these NSAIDs are forced to self-aggregate by increasing ionic strength: the CMC values found in these conditions are high and within this group of compounds further differences derive from the slope value of the solubilization plots, probably related to a different solubilization or aggregation mechanism (Fig. 4).

Above HHB = 1.5 we found alclofenac and fenbufen, whose anions display an overall hydrophilicity and are unable to solubilize the dye. The ability of these salt solutions to solubilize a hydrophobic probe may have important consequences when this behaviour is considered in an 'in vivo' system. Even if the experimental conditions, in which most of NSAIDs display solubilization ability, will never be found in vivo, this property can influence and modify their interaction with components of dosage form or components of membranes. At low concentrations, below CMC, surface active drug molecules can still be active to this respect: according to what is reported for bile salts (Fini, 1989), these molecules can insert within membranes: the interaction with membrane components brings consequences that could be positive in terms of the absorption rate of the drug itself, but also negative in terms of potential damage to the gastrointestinal membranes after oral administration. Because of the dilution by gastrointestinal fluids, NSAID can never be found in vivo above their critical concentrations, but molecules of this type could accumulate in the sites where dissolution occurs, starting from a solid dosage form, and there is the possibility that locally high concentrations can be achieved; moreover surface active drugs will inter-

act to form mixed micelles with other amphipathic substances such as lecithins or bile salts present in the physiological medium (Fini et al., 1993b).

These results suggest that high local concentrations of the NSAIDs should be avoided during oral administration, diluting the active principle with food or administering of the drug as a diluted aqueous solution. In this respect it is important to have available highly soluble chemical form or rapidly dissolving solid dosage forms.

Acknowledgements

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