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Kinetic Aspects of the Dissolution and Partition of Diclofenac, Alclofenac and Their Sodium Salts

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The dissolution and the three-phase partition profiles, *vs.* time, of diclofenac, alclofenac and their sodium salts have been examined in buffered mediums. The bioavailability of these drugs appears to be mainly controlled by the dissolution. The parameters influencing the higher dissolution rates of the sodium salts relative to the free acids are briefly discussed.

Kinetische Aspekte der Auflösung und Verteilung von Diclofenac, Alclofenac und ihren Natriumsalzen

Die Auflösung und die Dreiphasen Verteilungsprofile von Diclofenac, Alclofenac und ihren Natriumsalzen sind in Puffersystemen als Zeitfunktion untersucht worden. Die Bioverfügbarkeit dieser pharmazeutischen Stoffe scheint hauptsächlich von der Auflösung kontrolliert zu sein. Die Faktoren, die die hohe Auflösungsgeschwindigkeit der Natriumsalze gegenüber der der freien Säuren beeinflussen, werden kurz diskutiert.

It is widely accepted that absorption of any drug in a solid dosage form can be markedly influenced by its dissolution rate or by its partition behaviour in a w/o or w/o/w system.

In order to detect which of these properties could control in vitro absorption of some non steroidal antiinflammatory drugs (NSAID), investigations have been undertaken concerning the dissolution at physiological pH values and the partition rate in a three phase system (aqueous buffer/ n-octanol/aqueous buffer) of the most widely used NSAID both in the acidic and in the salt form[1,2].

In the present paper the behaviour of two well known arylacetic derivatives: diclofenac and alclofenac and their sodium salts has been examined.

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Experimental Part

Materials

The active principles examined were employed in powdered form. In order to obtain reliable and reproducible results the starting materials were milled in an analyticall mill*: samples having particle size distribution as close as possible were used throughout the experimental runs. The particle size distributions have been determined by the microscopic method and are reported in Table 1. The solutions used both in dissolution and partition tests were buffered according to *Sörensen*.

Table 1: *Physical properties of the drugs*

Drug	M.P. °C	Mean geom. diameter nm	Standard geom. deviation
Diclofenac (1)	156–158	14	1.8
Diclofenac Sodium (2)	283–285	12	1.6
Alclofenac (3)	92– 93	15.2	1.7
Alclofenac Sodium (4)	68– 70	16	1.9

[1] I.C.S., Milano I.

[2] I.C.S., Milano, I.

[3] gifted by Prof. *L. Cima*, Univ. of Padova, I.

[4] prepared from equimolecular amount of alclofenac and NaOH in EtOH by evaporation to dryness (quantitative yield), (MeOH – Et_2O).

Apparatus

The experimental conditions are similar to those previously described[1].

For dissolution tests a continuous flow apparatus was employed[3], since the linear flow velocity, as defined from the ratio flow rate/cross section is assumed to represent a realistic model of agitation in vivo.

Three-phase partition tests were carried out on a continuous flow w/o/w apparatus, fitted with a non-turbulent agitation of the phases, reported in Fig. 1.

Methods

Dissolution tests

The fluids employed were buffered at pH 2.0, 6.5, 8.0. The parameters describing each test are reported in Table 2.

The cumulative amount (mg) of each drug dissolved as a function of the time, Q_a and Q_s (Table 3), were calculated as previously described[1].

* analytical mill S1, Retsch, GmbH, W. Germany.

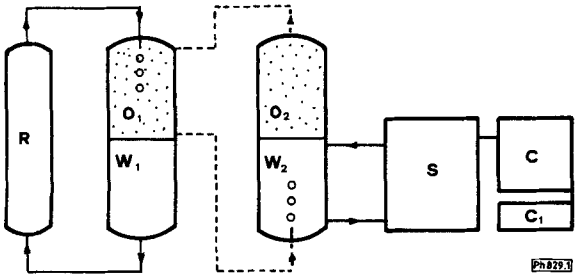

Fig. 1: Schematic drawing of the three-phase partition apparatus:
R = reservoir of the aqueous phase W_1; O_1, O_2 = oil phase (n-octanol); W_1, W_2 = aqueous (respectively releasing and receiving) phase; S = spectrophotometer operating with flow cells; C_1, C_2 = Computer control system (Apple II); → = aqueous fluxes (12 ml/min'); ⇢ = oil fluxes (12 ml/min').

Table 2: *Experimental parameters of dissolution tests*

Temp. (°C)	37	Flux F (ml/min)	12
Cell Vol. V (ml)	20	Amount of drug Q (mg)	50
Diameter D (cm)	3	Q / A (mg/cm²)	7.1
Section Area A (cm²)	7.1	F / A (ml/min · cm²)	1.7

Table 3: *Cumulative amount (mg) of drug dissolved, in the free (Qa) and in the salt form (Qs) after 500 min.*

Drug	pH = 2.0			pH = 6.5			pH = 8.0		
	Qa	Qs	Qs/Qa	Qa	Qs	Qs/Qa	Qa	Qs	Qs/Qa
Alclofenac	2			37			43		
			4.75			1.13			1.04
Alclofenac sodium		9.5			42			45	
Diclofenac	0.4			8			27		
			2.25			1.87			1.03
Diclofenac sodium		0.9			15			28	

Partition tests

Aqueous solutions (buffered at pH 2.0, 6.5, 8.0), n-octanol, aqueous buffer (pH 7.4) were the releasing, the lipidic and the receiving phase, resp. The first phase was $3 \cdot 10^{-5}$ M of each drug both in the free and salt form. Aqueous and organic phases were previously saturated by mechanical shaking and allow to equilibrate. The active principles in the receiving phase were detected spectrophotometrically at 276 nm (diclofenac) and 280 nm (alclofenac).

Results and Discussion

Dissolution tests

The dissolution profiles (mg of dissolved material) *vs* time in the pH range examined of diclofenac, alclofenac and their sodium salts are reported in Figures 2–4 and 5–7.

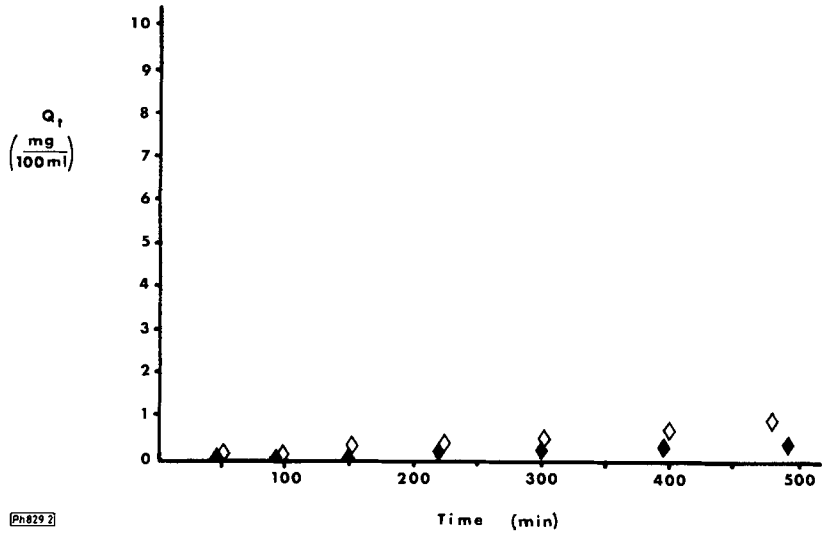

Fig. 2: Dissolution profiles at pH 2.0 of: ◆ diclofenac; ◇ diclofenac sodium

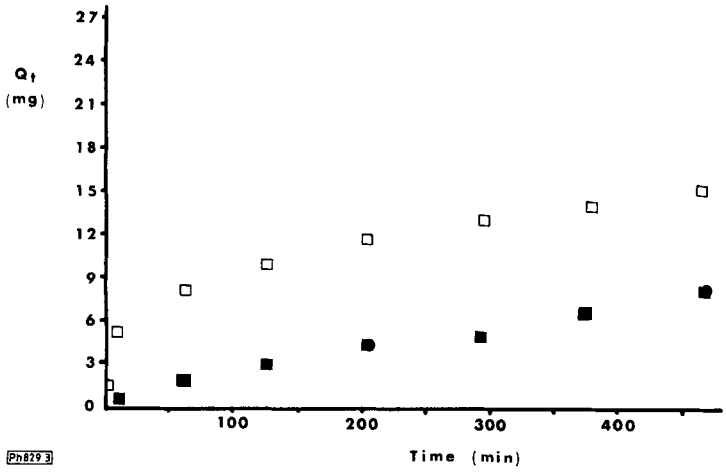

Fig. 3: Dissolution profiles at pH 6.5 of: ■ diclofenac, □ diclofenac sodium

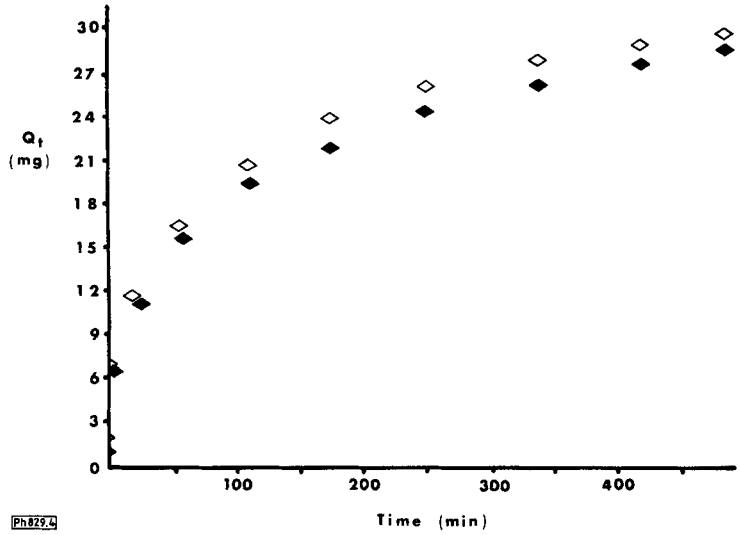

Fig. 4: Dissolution profiles at pH 8.0 of: ◆ diclofenac; ◇ diclofenac sodium

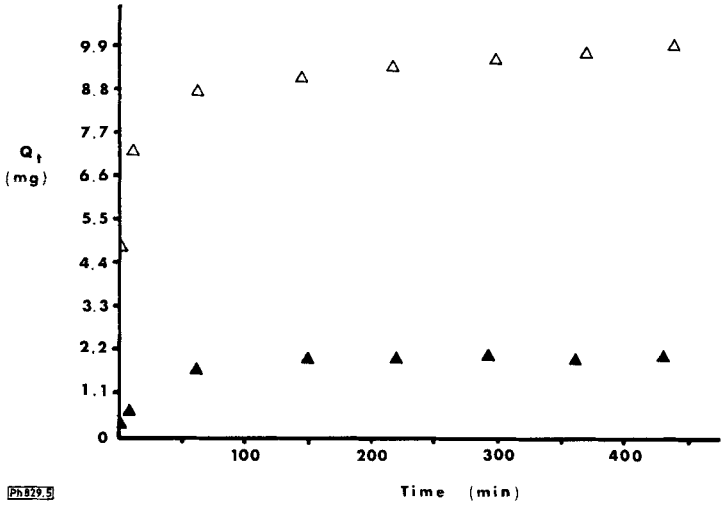

Fig. 5: Dissolution profiles at pH 2.0 of: ▲ alclofenac; △ alclofenac sodium

The cumulative amount of drug dissolved at time t = 500 min, Q are reported in Table 3, where Q_a is referred to the acidic form and Q_s to the salt form.

Data indicate that at each pH value of the dissolution medium the salt of both drugs show a higher dissolution rate when compared with the corresponding acidic form; this is further confirmed by the ratio Q_a/Q_s at the various pH values (Table 3).

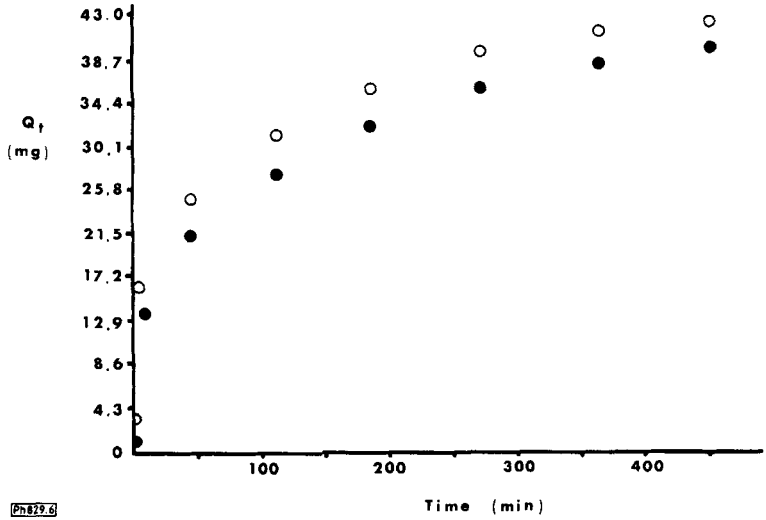

Fig. 6: Dissolution profiles at pH 6.5 of: ● alclofenac; ○ alclofenac sodium

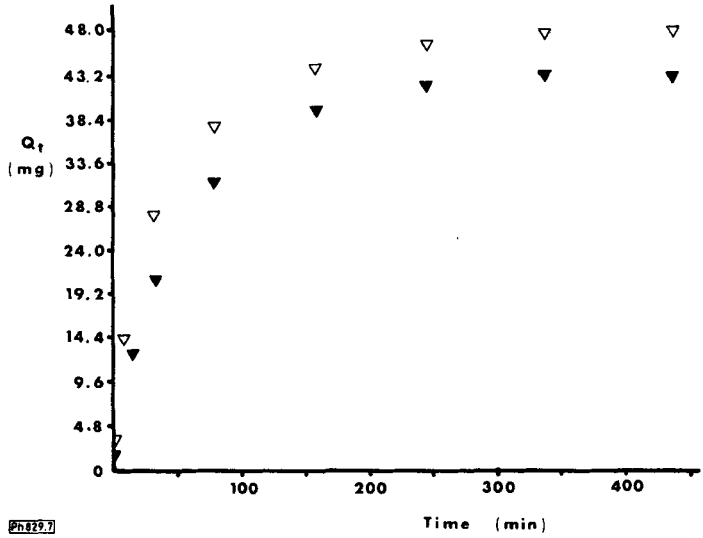

Fig. 7: Dissolution profiles at pH 8.0 of: ▼ alclofenac; ▽ alclofenac sodium

Partition tests

The figures 8 and 9 report the three-phase partition profiles of diclofenac and alclofenac and their sodium salts as a function of time: the plots show a high degree of linearity, by regressional analysis (r never less than 0.998); the slopes represent the partition rate constants k part.

The partition profiles at pH = 2.0 of diclofenac and its sodium salt have been not performed, owing to their low solubility in this medium.

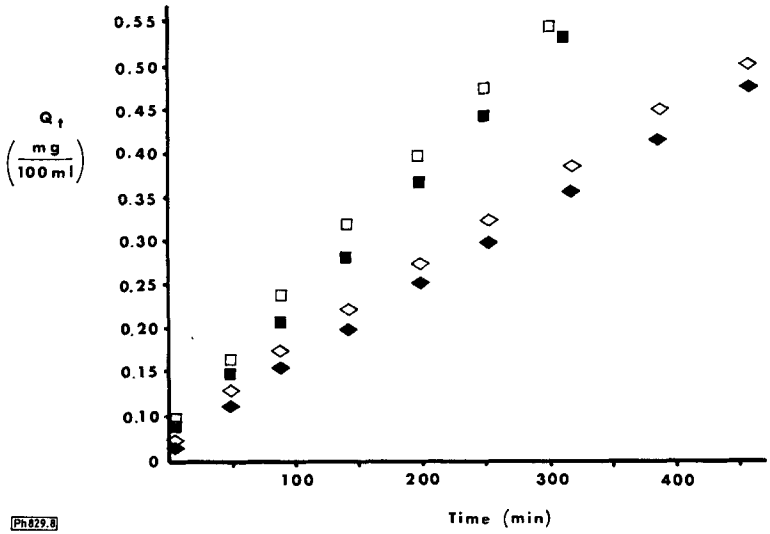

Fig. 8: Three-phase partition profiles of: ■◆ diclofenac; □◇ diclofenac sodium at different pH of the releasing phase

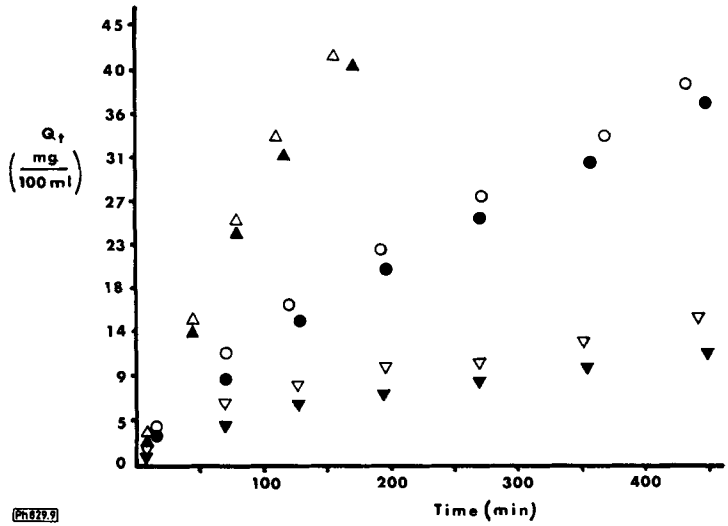

Fig. 9: Three-phase partition profiles of: ▲●▼ alclofenac; △○▽ alclofenac sodium at different pH of the releasing phase

The k part · values of the acidic and salt form of each drug do not differ more than the experimental uncertainty, as it appears from Table 4 and from Figure 10 where k part · values are reported *vs* the pH values of the releasing phase; these absorption profiles show, as expected, a faster rate in acidic medium, according to the relatively greater amount in this medium of the more lipophilic undissociated form.

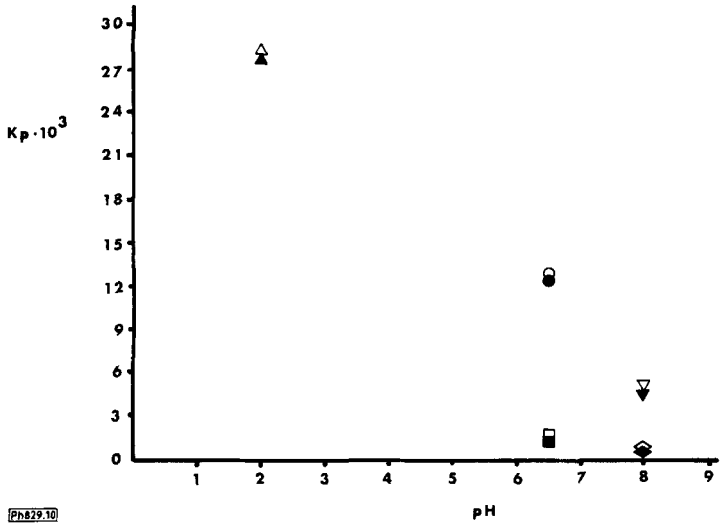

Fig. 10: Partition rate constants versus pH: ■◆ diclofenac; □◇ diclofenac sodium; ▲●▼ alclofenac; △○▽ alclofenac sodium.

Table 4: *Partition rate constants k part (mg/100 ml × min)*

Drug	pH = 2.0	pH = 6.5	pH = 8.0
Alclofenac	27.90	12.24	4.65
Alclofenac sodium	28.19	12.79	5.24
Diclofenac	—	$1.37 \cdot 10^{-3}$	$8.78 \cdot 10^{-4}$
Diclofenac sodium	—	$1.55 \cdot 10^{-3}$	$8.97 \cdot 10^{-4}$

Conclusions

The comparison of the dissolution and partition profiles of diclofenac, alclofenac and their sodium salts put in evidence faster dissolution rates and similar partition rates of the salts with respect to the free acids, in a pH range representing those likely to be encountered by the drug after oral administration.

These results qualitatively agree with those previously reported with naproxen[1] and *ibuprofen* and fenbufen[2] and seem to indicate that dissolution controls the bioavailability of these drugs from solid dosage forms.

The increase of the dissolution rate of the salts respect to the free acids may be ascribed to the higher solubility of the salt in the diffusive saturated microphase surrounding each solid particle[4], according to the theory of dissolution proposed by *Nernst* and *Brunner*[5].

However, as the dissolving solid acts as its own buffer,a pH gradient is expected in the liquid environment surrounding each particle towards the bulk solutions. So the

dissolution rate dc/dt depends on the solubility S_t of both the dissociated and the undissociated form of the drug at each local pH value.

Furthermore, S_t changes with the pH according to[6]:

$$S_t = S_0 (1 + 10^{pH-pKa})$$

A comparison between alclofenac (pKa = 4.29; S_0 at pH = 2.0 = $6.2 \cdot 10^{-5}$ M)[7] and diclofenac (pKa = 3.80, S_0 at pH 2.0 = $0.8 \cdot 10^{-5}$ M)[6] suggests that the last one at pH 2.0 has a greater amount of dissociated form, but that alclofenac improves its S_t value by means of a greater S_0 value: this results in a greater Q value (Tab. 3) for alclofenac with respect to diclofenac in both the forms at pH = 2.0.

These differences tend to disappear at higher pH values, where the dissociated form dominates.

The above considerations and the pH-dependent simulated absorption profiles (Fig. 10) seem to suggest higher and more rapidly reached blood levels after administration of the sodium salts of these drugs.

However, as far as the bioavailability of each sodium salt under investigation is concerned, it must be pointed out that also the pKa of the corresponding acid and its intrinsic solubility S_0 have to be taken into due account.

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