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# Modelling partitioning of sparingly soluble drugs in a two-phase liquid system

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**Abstract**

The aim of this work was to develop a proper mathematical model able to describe the kinetics partitioning of a drug between a polar (water buffer) and an apolar (*n*-octanol) liquid phase. In particular, attention is focussed on sparingly soluble drugs in one or both environments. Basically, we suppose that drug fluxes occurring between the polar and apolar phase depend also on drug solubility, and not only on both the kinetics constants and the instantaneous drug concentration in the two phases. The proposed model adequately describes the drug partitioning of sparingly water soluble drugs (piroxicam and nimesulide) as proven by the comparison of the predicted and experimental data. Moreover, it indicates the unsuitability of a previous approach (Chem. Pharm. Bull. 29 (1961) 2718) in describing the partitioning kinetics unless sink conditions in both phases are attained, this being difficult to achieve when working with sparingly soluble drugs. Consequently, the model represents a simple and reliable tool to study the drug partitioning kinetics. 

*Keywords:* Mathematical modelling; Partition coefficient; Sparingly soluble drug

## Nomenclature

| | |
|---|---|
| $a$ | model parameter (Eq. (12)) |
| $A$ | oil–water interface area |
| $b$ | model parameter (Eq. (13)) |
| $C^0$ | total drug concentration in the two-phases system (Eq. (20)) |
| $C_o$ | drug concentration in the oil phase |
| $C_o^{eq}$ | oil drug concentration at equilibrium |
| $C_{oi}$ | initial drug concentration in the oil phase |

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$C_{so}$ drug solubility in the oil phase
$C_{sw}$ drug solubility in the water phase
$C_w$ drug concentration in the water phase
$C_w^{eq}$ water drug concentration at equilibrium
$C_w^+$ dimensionless water drug concentration
$C_{weq}^+$ dimensionless water drug concentration at equilibrium
$C_{wi}$ initial drug concentration in the water phase
$C_{water}^{nime}$ nimesulide equilibrium concentration in water
$C_{water}^{piro}$ piroxicam equilibrium concentration in water
$f$ model parameter (Eq. (14))
$F_{ow}$ oil–water drug flux
$F_{wo}$ water–oil drug flux
$k_{ow}$ oil–water rate partition constant
$k_{wo}$ water–oil rate partition constant
$k_o^{obs}$ observed rate constant (Eq. (1))
$k_w^{obs}$ observed rate constant (Eq. (1))
$M_0$ total drug amount present in the two-phases system
$P$ partition coefficient
$P_a$ apparent partition coefficient
$R_c$ ratio between $C_{weq}^+$ calculated according to Eq. (7) and the new model
$R_k$ water–oil/oil–water rate constants ratio (Eq. (23))
$R_v$ water volume/oil volume ratio (Eq. (23))
$t$ time
$t^+$ dimensionless time
$V_o$ oil phase volume
$V_w$ water phase volume
$\alpha$ solubility ratio
$\beta$ parameter (Eq. (22))
$\delta$ parameter (Eq. (22))

## 1. Introduction

A detailed study of drug partitioning between a polar (water buffer) and an apolar (*n*-octanol) environment is very important since some drug physicochemical properties and in vivo behaviour can be determined on the basis of this phenomenon. In particular, the drug partition coefficient $P$, strictly connected to drug lipophilicity, has a paramount importance in predictive environmental studies (Finizio et al., 1997) as it is used in evaluative models for prediction of distribution among environmental compartments (Coehn et al., 1982), in equations for the estimation of bioaccumulation in animals and plants (Briggs et al., 1982) and in predicting the toxic effects of a substance (Calamari and Vighi, 1990). Moreover, while lipophilicity encodes a wealth of structural information (El Tayar et al., 1992), especially in oral or parenteral administrations, the drug effectiveness can strongly depend on $P$ (Lung et al., 1987). Indeed, usually, the drug has to cross the lipophilic cell barriers (Camenish et al., 1996; Mertin and Lippold, 1997; Camenish et al., 1998a,b) to get to its therapeutic target.

So, the simplest way for in vitro schematising this physiological condition is the employment of a two-phase environment into which the drug distributes (Fini et al., 1986; Nook et al., 1987; Grundy et al., 1996; Hoa and Kinget, 1996; Polli,

1996; Grundy et al., 1997a,b; Shlyankevich et al., 1998). Additionally, the study of a two-phase system can furnish useful information on the behaviour of drug release from disperse systems such as emulsions and microemulsions (Grassi et al., 2000).

Although it is now possible to estimate $P$ by means of different approaches (Leo, 1993; Testa et al., 1996; Breindl et al., 1997; Beck et al., 2000), its experimental determination is still a common technique (Banerjee et al., 1980; Yalkowsky et al., 1983; Gobas et al., 1988; Petterson-Nordén et al., 1997). Consequently, the experimental study of the apolar–polar phase drug partitioning assumes a very important role in the pharmaceutical field and that is why its mathematical description needs a particular care. The aim of this paper is to experimentally and mathematically analyse the kinetics of drug partitioning in order to develop a proper and reliable laboratory tool to compare important physicochemical characteristics of different drugs.

## 2. Modelling

The experimental set up is schematically shown in Fig. 1. The upper apolar phase is initially drug free, while the lower water phase contains a known drug amount giving origin to a concentration gradient between the two phases. Mixing conditions inside each phase are guaranteed by an impeller connected with a metallic rotating rod whose rotational speed is set to prevent apolar–polar phase mixing at the interface. The temperature of the whole system is kept constant by means of a surrounding thermostatic water bath.

Drug concentration in the polar phase (water) is continuously measured and recorded by means of an on-line (computer managed) UV spectrophotometer connected to the two-phase system and to a re-circulating peristaltic pump. In this manner we avoid the perturbation of the whole system due to sampling.

Drug transfer between the two phases can be described by means of a three step mechanism (Waterbeemd van de et al., 1981): a diffusion controlled step towards the interface, a de- and re-solvation step at the interface and, finally, a new diffusion controlled step. Indeed, the transfer from the first phase to the second one requires the drug molecules to diffuse through a stagnant layer preceding the theoretical interface. Then, an energy step, allowing the drug molecules passage from the first solvent to the second, occurs. Finally, a diffusion controlled step away from interface develops (Waterbeemd van de et al., 1980).

The kinetics of this mechanism can be represented by means of a series of three first-order chemical reactions in which the products of the first reaction become reagents of the second one and so on. Thus, the mathematical description of the kinetics requires us to write down four differential rate equations for reactants, products and intermediates (Waterbeemd van de et al., 1981). Nevertheless, if the steady-state treatment is considered (Waterbeemd van de et al., 1980), the system of differential equations reduces to:

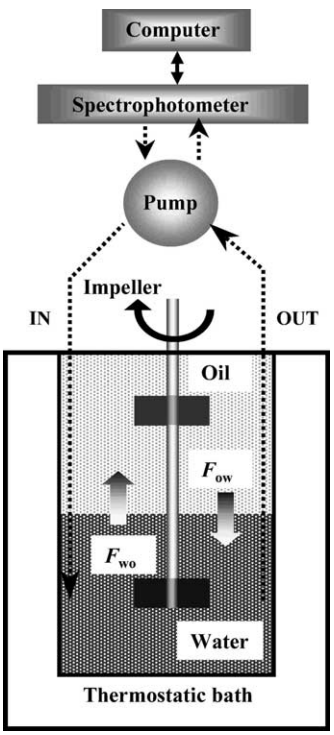


Fig. 1. Experimental set up to be modelled. The drug moves from the lower water phase to the upper oil phase due to an initial concentration gradient.

$$\frac{dC_w}{dt} = k_o^{obs} C_o - k_w^{obs} C_w \quad (1)$$

$$C_o = \frac{M_0 - V_w C_w}{V_o} \quad (2)$$

where $t$ is time, $C_o$ and $C_w$ are the drug concentrations in the apolar and polar phase, respectively, $k_o^{obs}$ and $k_w^{obs}$ are the observed rate constants (Waterbeemd van de et al., 1980): for each phase, $V_o$ and $V_w$ are the volume of the apolar and polar phase, respectively, and $M_0$ is the total, and constant, drug amount present in the two-phase system. While Eq. (1) is the only rate equation (steady-state hypothesis), Eq. (2) is nothing more than a drug mass balance (made up on the two-phase system) allowing the determination of $C_o$ dependence on $C_w$. Basically, this is also the approach followed by Lippold and Waterbeemd (Lippold and Schneider, 1975, 1976; Waterbeemd van de et al., 1978), although they studied the kinetics of a more complex partition experiment in which two polar phases and one apolar phase were involved. Moreover, Takayama (Takayama et al., 1961) described the drug partitioning by means of Eq. (1), but did not confer a detailed meaning to $k_o^{obs}$ and $k_w^{obs}$.

Eq. (1) can be formally expressed in a different way if we define as follows the drug fluxes occurring between the apolar and polar phase:

$$F_{ow} = k_{ow} C_o \quad (3)$$

$$F_{wo} = k_{wo} C_w \quad (4)$$

where $F_{ow}$ and $F_{wo}$ represent, respectively, the drug flux from the apolar phase to the polar one and vice-versa, while $k_{ow}$ and $k_{wo}$ are the rate constants, dimensionally a velocity, characterising $F_{ow}$ and $F_{wo}$, respectively. Thus, Eq. (1) can be rewritten as:

$$\frac{dC_w}{dt} = \frac{AF_{ow}}{V_w} - \frac{AF_{wo}}{V_w} = \frac{Ak_{ow}}{V_w} C_o - \frac{Ak_{wo}}{V_w} C_w \quad (5)$$

where $A$ is the interface area. Consequently, the following relations hold:

$$k_o^{obs} = \frac{Ak_{ow}}{V_w} \qquad k_w^{obs} = \frac{Ak_{wo}}{V_w} \quad (6)$$

Bearing in mind Eq. (2), the solution of Eq. (5) is (Demidovic, 1975):

$$C_w = \frac{k_{ow} M_0}{k_{wo} V_o + k_{ow} V_w} - \left( \frac{k_{ow} M_0}{k_{wo} V_o + k_{ow} V_w} - C_{wi} \right) e^{\left( -A \frac{k_{wo} V_o + k_{ow} V_w}{V_o V_w} t \right)} \quad (7)$$

where $C_{wi}$ is the initial drug concentration in the polar phase.

Although Eq. (7) represents a milestone in the pharmaceutical field as it gave a great contribution in the interpretation of the drug partitioning phenomenon, it can not be applied in the case of sparingly soluble drugs in one or both phases. In this situation, indeed, as later on proven, Eq. (7) can yield to $C_w$ values greater than the drug water solubility $C_{sw}$ as a direct consequence of its mathematical nature. Consequently, Eq. (7) can be properly used only for describing the partitioning of sufficiently soluble drugs in both environments. It is worthwhile remembering that these conditions are not satisfied when working, for instance, with the widely used non-steroidal anti-inflammatory drugs. Indeed, these substances are generally soluble in an apolar phase while they are sparingly soluble in a polar phase. In this light, we propose an empirical, but reasonable, modification of $F_{ow}$ and $F_{wo}$ in order to properly take into account the above mentioned solubility problem. Accordingly, $F_{ow}$ and $F_{wo}$ can be modified in the following manner:

$$F_{ow} = k_{ow} C_o \left( \frac{C_{sw} - C_w}{C_{sw}} \right) \quad (8)$$

$$F_{wo} = k_{wo} C_w \left( \frac{C_{so} - C_o}{C_{so}} \right) \quad (9)$$

where $C_{so}$ and $C_{sw}$ are the drug solubility in the apolar and polar phase, respectively. It is clear that as $F_{ow}$ and $F_{wo}$ vanish when $C_w$ and $C_o$ approach $C_{sw}$ and $C_{so}$, respectively, the proposed model will never yield $C_o$ and $C_w$ values greater then their solubility threshold. Interestingly, Eq. (8) and Eq. (9) reduce to Eq. (3) and Eq. (4) when $C_w$ and $C_o$ are well below $C_{sw}$ and $C_{so}$, respectively. In this sense, our new model proposes as a generalisation of the previous one (Eq. (7)) showing the same advantages but avoiding the drawbacks.

The new model kinetics is then obtained by solving (Demidovic, 1975) the following system:

$$\frac{dC_w}{dt} = \frac{AF_{ow}}{V_w} - \frac{AF_{wo}}{V_w} \tag{10}$$

$$C_o = \frac{M_0 - V_w C_w}{V_o}$$

where $F_{ow}$ and $F_{wo}$ are now given by Eq. (8) and Eq. (9). Inserting Eq. (2) into Eq. (10), we get:

$$\frac{dC_w}{dt} = C_w^2 a + C_w b + f \tag{11}$$

where:

$$a = \frac{A}{V_o}\left(\frac{k_{ow}}{C_{sw}} - \frac{k_{wo}}{C_{so}}\right) \tag{12}$$

$$b = A\left(\frac{k_{wo}}{C_{so}V_w}\left(\frac{M_0}{V_o} - C_{so}\right) - \frac{k_{ow}}{C_{sw}V_o}\left(\frac{M_0}{V_w} + C_{sw}\right)\right) \tag{13}$$

$$f = Ak_{ow}\frac{M_0}{V_w V_o} \tag{14}$$

Depending on the $a$, $b$ and $f$ values, Eq. (11) can be solved by means of usual techniques (Demidovic, 1975) to yield:

*case 1:* $a > 0$ and $|b| < 2\sqrt{af}$

$$C_w = \left(\frac{\sqrt{f - b^2/4a}}{\sqrt{a}}\right) \times \frac{(\sqrt{f - b^2/4a})\mathrm{tg}(t\sqrt{a}\sqrt{f - b^2/4a}) + \sqrt{a}(C_{wi} + b/2a)}{\sqrt{f - b^2/4a} - \sqrt{a}(C_{wi} + b/2a)\mathrm{tg}(t\sqrt{a}\sqrt{f - b^2/4a})} \tag{15}$$

*case 2:* $a > 0$ and $|b| > 2\sqrt{af}$

$$C_w = \left(\frac{\sqrt{(b^2/4a) - f}}{\sqrt{a}}\right) \times \frac{1 + \dfrac{\sqrt{a}(C_{wi} + b/2a) - \sqrt{(b^2/4a) - f}}{\sqrt{a}(C_{wi} + b/2a) + \sqrt{(b^2/4a) - f}} e^{(2t\sqrt{(b^2/4a) - f}\sqrt{a})}}{1 - \dfrac{\sqrt{a}(C_{wi} + b/2a) - \sqrt{(b^2/4a) - f}}{\sqrt{a}(C_{wi} + b/2a) + \sqrt{(b^2/4a) - f}} e^{(2t\sqrt{(b^2/4a) - f}\sqrt{a})}} - \frac{b}{2a} \tag{16}$$

*case 3:* $a = 0$

$$C_w = \left(\frac{f}{b} + C_{wi}\right)e^{(bt)} - \frac{f}{b} \tag{17}$$

case 4: $a < 0$

$$C_w = \left(\frac{\sqrt{f - (b^2/4a)}}{\sqrt{-a}}\right) \times \frac{1 + \dfrac{\sqrt{-a}(C_{wi} + b/2a) - \sqrt{f - (b^2/4a)}}{\sqrt{-a}(C_{wi} + b/2a) + \sqrt{f - (b^2/4a)}} e^{(-2t\sqrt{f - (b^2/4a)}\sqrt{-a})}}{1 - \dfrac{\sqrt{-a}(C_{wi} + b/2a) - \sqrt{f - (b^2/4a)}}{\sqrt{-a}(C_{wi} + b/2a) + \sqrt{f - (b^2/4a)}} e^{(-2t\sqrt{f - (b^2/4a)}\sqrt{-a})}} - \frac{b}{2a} \tag{18}$$

The fact that the model assumes different expressions depending on the parameter values, is not very good especially when performing a data fitting. Indeed, usually, it is not a trivial task to a priori know whether $a \leqslant 0$ or $a > 0$. However, this problem can be overcome by embodying Eq. (15)–Eq. (18) into a proper routine that automatically selects the correct model expression (Grassi, 2000).

## 3. Materials and methods

Piroxicam (Chiesi, Parma, Italy) and Nimesulide (Helsinn, Pambio-Noranco Lugano, Switzerland) are chosen as model drugs for their low water solubility and for the fact that their water solubility is pH dependent.

### 3.1. Partition: kinetics

Two different kinds of experimental conditions are considered: in the first case the polar phase is water buffered at pH 1.2 saturated with *n*-octanol (Poole, BH15 1TD, England) (from now on the polar phase will be termed 'water phase') while the apolar phase is represented by *n*-octanol saturated with water buffered at pH 1.2 (from now on this phase will be termed 'oil phase'). In the second case we have water buffered at pH 7.5 saturated with *n*-octanol and *n*-octanol saturated

Table 1
Characteristics of the four different kinds of partition experiments performed

| pH | 1.2 | 7.5 |
|---|---|---|
| *Piroxicam* | | |
| | Test 1 | Test 2 |
| $k_{wo}$ (cm/s) | $(2.52 \pm 0.007) \times 10^{-3}$ | $(3.63 \pm 0.02) \times 10^{-4}$ |
| $k_{ow}$ (cm/s) | $(2.85 \pm 0.02) \times 10^{-4}$ | $(8.25 \pm 0.06) \times 10^{-4}$ |
| $C_{sw}$ (μg/cm$^3$) | $250 \pm 3.47$ | $2171 \pm 4.8$ |
| $C_{so}$ (μg/cm$^3$) | $1683 \pm 57$ | $1653 \pm 38$ |
| $C_{wi}$ (μg/cm$^3$) | $15.2 \pm 0.2$ | $21.8 \pm 0.5$ |
| $P(-)$ | 8.8 | 0.44 |
| *Nimesulide* | | |
| | Test 3 | Test 4 |
| $k_{wo}$ (cm/s) | $(2.29 \pm 0.01) \times 10^{-3}$ | $(1.1 \pm 0.003) \times 10^{-3}$ |
| $k_{ow}$ (cm/s) | $(2.85 \pm 0.2) \times 10^{-5}$ | $(5.3 \pm 0.2) \times 10^{-5}$ |
| $C_{sw}$ (μg/cm$^3$) | $11.8 \pm 0.5$ | $104 \pm 12$ |
| $C_{so}$ (μg/cm$^3$) | $2789 \pm 46$ | $2702 \pm 22$ |
| $C_{wi}$ (μg/cm$^3$) | $8.5 \pm 0.3$ | $45 \pm 2$ |
| $P(-)$ | 80.4 | 20.7 |

with water buffered at pH 7.5. The pre-saturation of both the two phases is required to prevent *n*-octanol migration into the water phase and vice-versa. Indeed, this could probably affect the drug solubility in the two phases during the partitioning experiment. This pre-saturation is performed by adding equal volumes of *n*-octanol and water, at each pH, in a well-stirred thermostatic sealed vessel for 24 h. Then, the two-phase system is let to rest until the separation has been attained ($\approx 4$ h) in order to physically separate the oil phase from the aqueous one. Thus, piroxicam and nimesulide solubility (Table 1) is measured in each of the pre-saturated phases at 37 °C, this being the temperature of the partitioning tests.

The aqueous phase has a volume $V_w = 150$ cm$^3$, the oil phase is characterised by a volume $V_o = 50$ cm$^3$ while the interfacial area $A = 34$ cm$^2$. Initially, the oil phase is drug free, while the aqueous phase is characterised by a drug concentration $C_{wi}$ (Table 1). Drug concentration decrease in the aqueous phase is monitored and recorded by means of an on-line UV spectrophotometer (UV spectrophotometer, Lambda 6/PECSS System, Perkin-Elmer Corporation, Norwalk, CT. Wavelength: Piroxicam pH 1.2 = 354.2 nm; Piroxicam pH 7.5 = 352.6 nm; Nimesulide pH 1.2 = 300 nm; Nimesulide pH 7.5 = 390 nm). Fluid re-circulation is ensured by a peristaltic pump (Fig. 1). Each test is performed in triplicate.

### 3.2. Partition: equilibrium

Having completed the two-phase pre-saturation (water phase buffered at pH 1.2) as indicated above, a known amount of drug (1300 μg piroxicam; 750 μg nimesulide) is placed in the water phase (75 cm$^3$ piroxicam case; 90 cm$^3$ nimesulide case) in order to get approximately the same initial concentration of the kinetics test ($C_{wi}$ of test 1 for Piroxicam and $C_{wi}$ of test 3 for Nimesulide, see Table 1). These aqueous solutions are then, respectively, mixed with 25 cm$^3$ (piroxicam case) or 10 cm$^3$ (nimesulide case) pre-saturated, drug free, oil phase and the whole system is put in a well-stirred thermostatic (37 °C) sealed vessel for 48 h. After the two-phase system separation (4 h), drug concentration in the water phase is measured ($C^{nime}_{water} = 0.81 \pm 0.06$ μg/cm$^3$; $C^{piro}_{water} = 4.6 \pm 0.16$ μg/cm$^3$; UV spectrophotometer, Lambda 6/PECSS System, Perkin-Elmer Corporation. Wavelength: Piroxicam pH 1.2 = 354.2 nm; Nimesulide pH 1.2 = 300 nm). The oil drug concentration, $C^{eq}_o$, is determined on the basis of a drug balance made up on the whole system (oil and water phase). Finally, the partition coefficient is determined as the ratio $C^{eq}_o/C^{eq}_w$.

## 4. Results and discussion

Before presenting the experimental results, it is interesting to compare Eq. (7) with the new model in the particularly significant case of mass transfer from a drug loaded oil phase (initial drug concentration $C_{oi}$) to a drug free aqueous phase. To get a wider generality, the following variables will be considered:

$$t^+ = k_{wo}\frac{tA}{V_o + V_w} \qquad C^+_w = \frac{C_w}{C_{sw}} \tag{19}$$

where $t^+$ and $C_w^+$ are, respectively, dimensionless time and water drug concentration. Moreover, in order to be close to our experimental conditions (see Table 1, test 3 conditions), we assume $C_{so} = 2500\ \mu g/cm^3$, $C_{sw} = 10\ \mu g/cm^3$, $k_{ow} = 10^{-5}$ cm/s; $k_{wo} = 10^{-3}$ cm/s, $V_o = 50\ cm^3$, $V_w = 150\ cm^3$, $A = 34\ cm^2$. Fig. 2 shows the comparison between $C_w^+$ trend according to Eq. (7) and the new model in the case of $C_{oi}/C_{so} = 0.5$ (Eq. (7), upper solid line; new model, upper thin dashed line) and $C_{oi}/C_{so} = 0.4$ (Eq. (7), lower solid line; new model, lower thin dashed line). Beside the evident discrepancies arising between the two models, whatever the $C_{oi}/C_{so}$ considered, it is interesting to notice that, in the $C_{oi}/C_{so} = 0.5$ case, Eq. (7) erroneously predicts an exceeding of the drug solubility ($C_w^+$ exceeds 1). This meaningless prediction clearly reveals the unsuitability of Eq. (7) in describing the oil–water partition of sparingly water-soluble drugs. Additionally, it is worthwhile mentioning the fact that this unsuitability mainly manifests itself when the overall drug concentration in the two-phase environment is high. Indeed, for low concentration values, $C_{sw}$ and $C_{so}$ can be regarded as infinitely large and it is easy to verify that the $F_{ow}$ and $F_{wo}$ definition, according to Eq. (8) and Eq. (9), reduce to that given by Eq. (3) and Eq. (4). To better define the boundary over which Eq. (7) becomes unsuitable, Fig. 3 reports

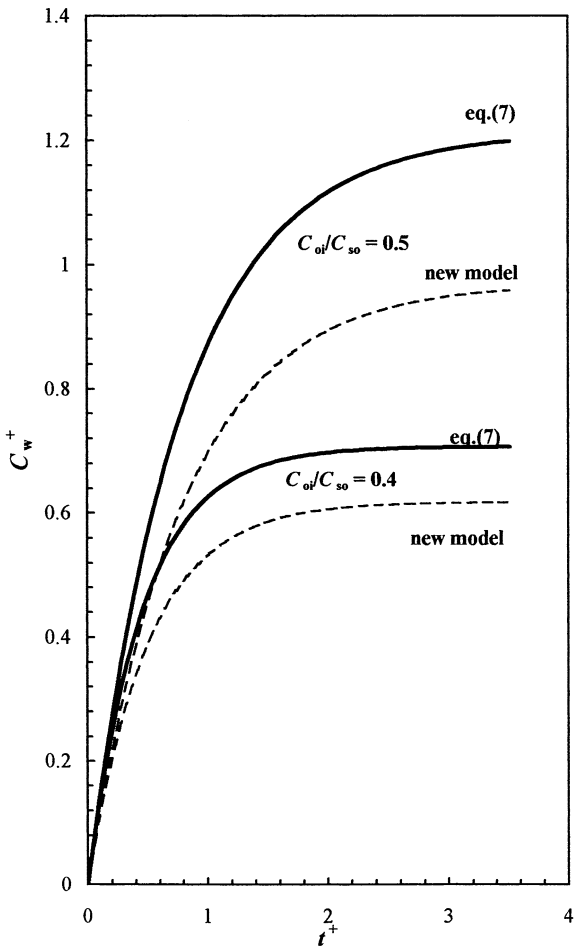


Fig. 2. Dimensionless aqueous concentration ($C_w^+$) versus dimensionless time $t^+$ calculated according to Eq. (7) (solid lines) and to the new model (thin dashed lines) considering two different values of the ratio $C_{oi}/C_{so}$.

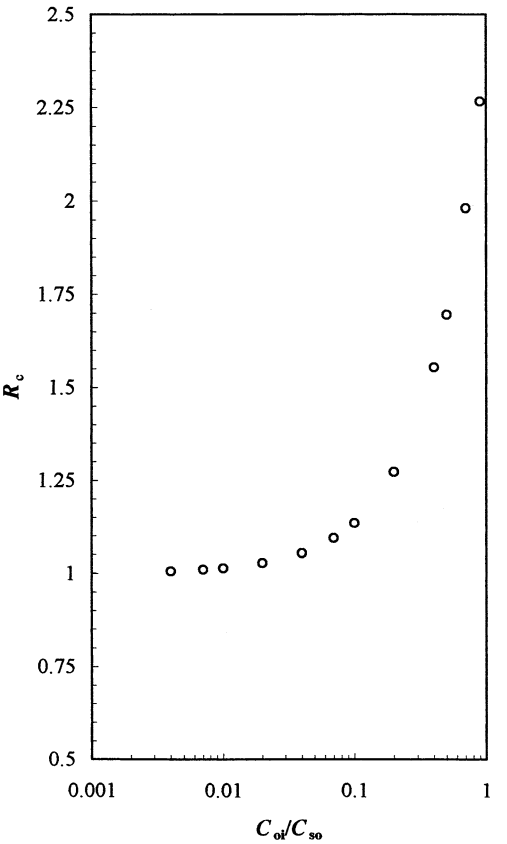


Fig. 3. Dependence of $R_c$ parameter (ratio between the equilibrium $C_w^+$ value calculated according to Eq. (7) and the new model) on the ratio $C_{oi}/C_{so}$. As soon as $C_{oi}/C_{so}$ increases, $R_c$ goes away from the correct unitary value.

the ratio $R_c$ (it is the ratio between the equilibrium $C_w^+$ value ($C_{weq}^+$) calculated according to Eq. (7) and to new model) versus the ratio $C_{oi}/C_{so}$ (same parameter values of Fig. 2). Wherever $R_c$ is close to one when $C_{oi}/C_{so}$ is lower then 0.07 (in this case the two models do not substantially differ), for higher values, $R_c$ increases being absolutely greater then one. Accordingly, as Eq. (7) correctly works only in the limit of zero drug concentration in the two-phase system, the new model results a generalisation of Eq. (7).

In order to check the reliability and the correctness of the developed model, two sparingly water soluble drugs are considered: Piroxicam (low water soluble) and Nimesulide (very low water soluble). Moreover, as their solubility is pH dependent, partitioning tests are performed using two different aqueous media (buffered at pH 1.2 and 7.5). *n*-Octanol constitutes the oil phase because of its large employ in the partitioning tests (Mackay et al., 1980; Yalkowsky and Valvani, 1980; Gobas et al., 1988; Camenish et al., 1996) despite its poor representation of the lipophilic environment met in vivo (Ottinger and Wunderli-Allenspach, 1997). Of course, as partitioning experiments are performed by saturating in advance the oil phase with the aqueous phase and vice-versa, the drug solubility values reported in this work refer to an oil-saturated aqueous phase and to an aqueous medium-saturated oil phase (Table 1).

Fig. 4, referring to test 1 (piroxicam partition pH 1.2, see Table 1) shows the very good agreement between the experimental data (open circles) and the model best fitting (solid line). This evidence ensures that the model is able to well represent the phenomena ruling piroxicam partition kinetics between the two phases. Analogously, Fig. 5, referring to test 2 (piroxicam partition pH 7.5, see Table 1), reports the very good data fitting (open circles) performed by the model (solid line). It is interesting to notice that the pH reduction determines approximately one order of magnitude decrease of the aqueous piroxicam solubility (but almost constant oil solubility) with a considerable increase of $k_{wo}$ and a $k_{ow}$ reduction. This behaviour could be ascribed to the fact that at pH 1.2 Piroxicam (weak acid, $pK_a =$ 6.3 (Wiseman and Lombardino, 1982)) is less dissociated than at pH 7.5 and the affinity for the aqueous phase is bigger for its dissociated form.

Fig. 6, referring to test 3 (nimesulide partition pH 1.2, see Table 1), and Fig. 7, referring to test 4 (nimesulide partition pH 7.5, see Table 1), again show a very good agreement between the experimental data (open circles) and the model best fitting (solid line). This is a further confirmation of the suitability of the model's description of the phenomena ruling the drug partitioning between the oil and the aqueous phase. Also in this case, pH reduction causes an order magnitude decrease of the nimesulide aqueous solubility (while its oil solubility is almost the same) while $k_{wo}$ and $k_{ow}$

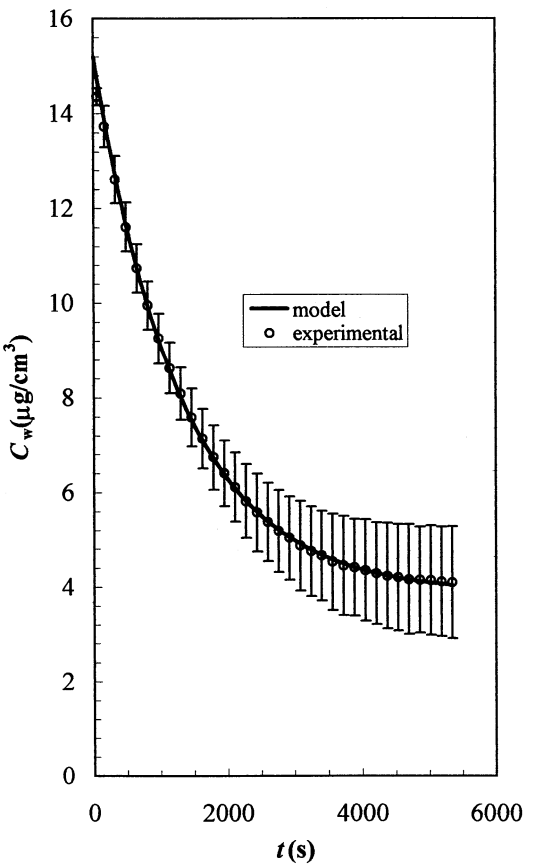


Fig. 4. Comparison between model best fitting (solid line) and experimental data (open circles; vertical bar indicates datum standard error) in the case of piroxicam partition pH 1.2 (test 1 conditions).

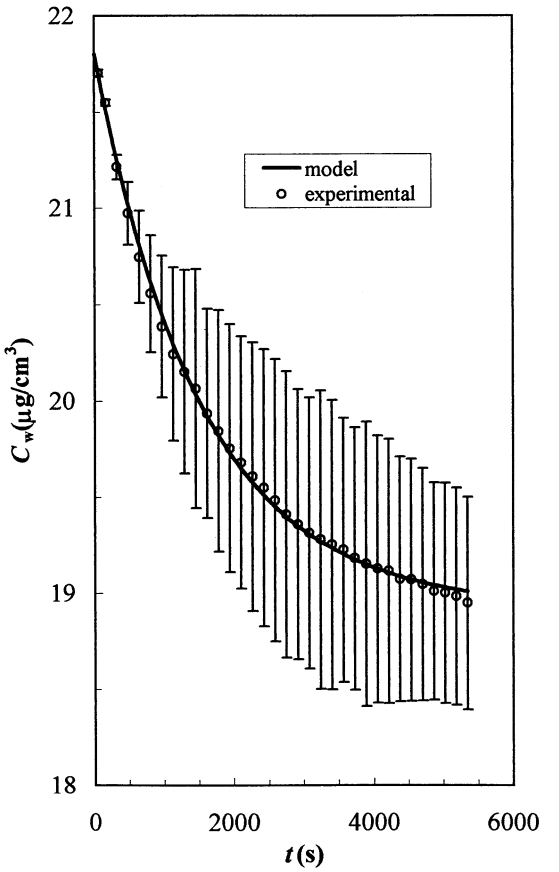


Fig. 5. Comparison between model best fitting (solid line) and experimental data (open circles; vertical bar indicates datum standard error) in the case of piroxicam partition pH 7.5 (test 2 conditions).

are not heavily affected by the pH variation. It is interesting to notice that the reliability of both our experimental and theoretical approach can be also evaluated through the low fitting parameters ($k_{ow}$, $k_{wo}$) standard deviation (Table 1). Indeed, this information comprehends both data variability (see error bars reported in Fig. 4–Fig. 7; the apparent different entity of error bars in those figures is due to different scale amplitude) and model fitting skill. Only in case of high fitting parameters standard deviation, we should doubt of our analysis.

On the basis of the new proposed model, we can also see how drug partitioning depends on the initial drug concentration $C^0$ in the two-phase system. For this purpose, let us define $C^0$ and the apparent partition coefficient $P_a$ as follows:

$$P_a = \frac{C_o^{eq}}{C_w^{eq}} \qquad C^0 = \frac{V_w C_{wi} + V_o C_{oi}}{V_w + V_o} \tag{20}$$

where $C_o^{eq}$ and $C_w^{eq}$ represent, respectively, the oil and water drug concentration at equilibrium, while $C_{oi}$ is the initial oil drug concentration. The $P_a$ dependence on $C^0$ can be get remembering that, at equilibrium $F_{ow} = F_{wo}$ (Eqs. (8) and (9)) and $C_o$ depends on $C_w$ according to Eq. (2). Consequently, we get:

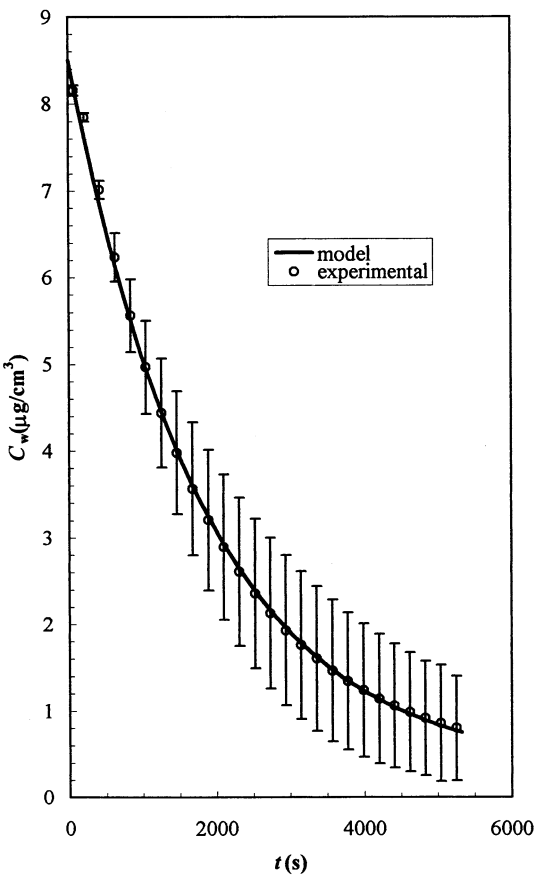


Fig. 6. Comparison between model best fitting (solid line) and experimental data (open circles; vertical bar indicates datum standard error) in the case of nimesulide partition pH 1.2 (test 3 conditions).

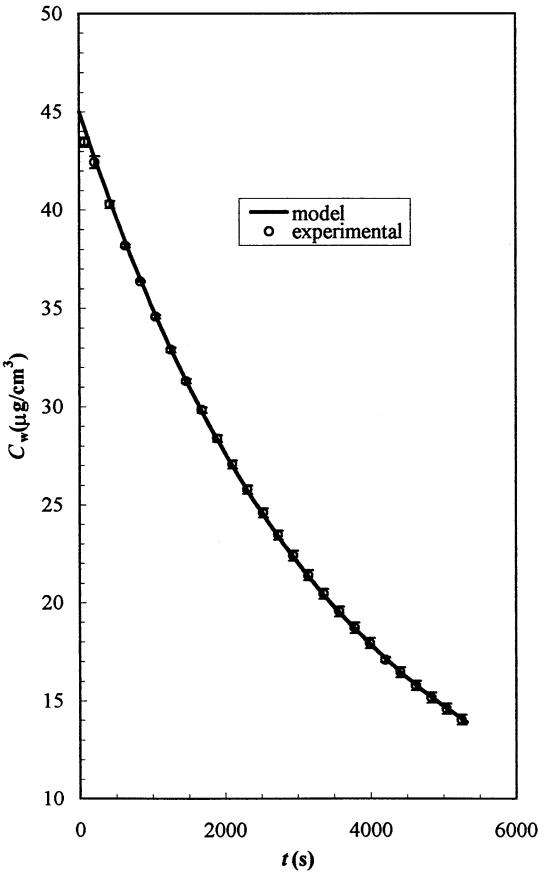


Fig. 7. Comparison between the model best fitting (solid line) and the experimental data (open circles; vertical bar indicates datum standard error) in the case of nimesulide partition pH 7.5 (test 4 conditions).

$$P_a = R_k\left(\frac{C_{so} - C^0(R_v+1) + C_w^{eq}R_v}{(C_{sw} - C_w^{eq})\alpha}\right)$$

$$C_w^{eq} = -\frac{\beta}{2} \pm \sqrt{\left(\frac{\beta}{2}\right)^2 - \delta} \qquad (21)$$

where

$$\beta = -\left(\frac{C_{so}R_k}{(\alpha - R_k)R_v} + \frac{\alpha C_{sw}}{(\alpha - R_k)} + \frac{C^0(1+R_v)}{R_v}\right);$$

$$\delta = \frac{\alpha C_{sw}(1+R_v)}{(\alpha - R_k)R_v}C^0 \qquad (22)$$

$$R_v = \frac{V_w}{V_o} \qquad R_k = \frac{k_{wo}}{k_{ow}} \qquad \alpha = \frac{C_{so}}{C_{sw}} \qquad (23)$$

Fig. 8 shows the $P_a$ dependence on $C^0$ in the hypothesis of setting $R_v = 3$, $C_{sw} = 10$ μg/cm$^3$, $C_{so} = 2000$ μg/cm$^3$, and different $R_k$ values. It is clear that for $R_k \neq \alpha$, $P_a$ strongly depends (in an almost linear manner) on $C^0$, and, in particular, for $R_k = 10\alpha$ (thickest line) it decreases with $C^0$, while for $R_k = 0.1\alpha$ (thinnest line) it increases with $C^0$. This predicted behaviour finds its physical justification in the fact that if $R_k > \alpha$, this implying $k_{wo} > k_{ow}$, a $C^0$ reduction implies a more pronounced drug impoverishment of the water phase than that of the oil phase, while, for $R_k < \alpha$, this implying $k_{wo} < k_{ow}$, the opposite phenomenon takes place. Thus, when $R_k$ approaches $\alpha$, a $C^0$ reduction determines an equal drug impoverishment of both the water and the oil phase, so that

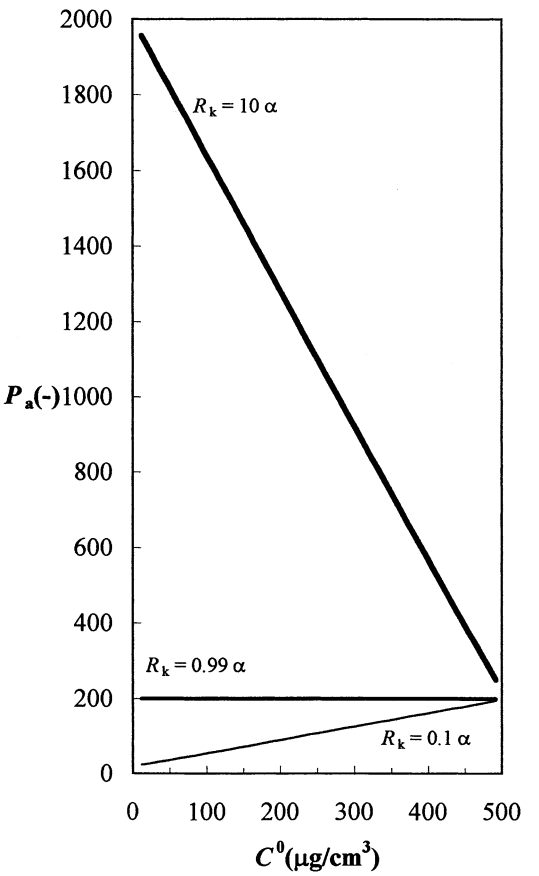


Fig. 8. Apparent drug partition coefficient $P_a$ dependence on the total drug concentration $C^0$ in the two-phase system for three different $R_k$ values.

$P_a$ remains constant and its value coincides with that of the oil–water drug solubility ratio ($\alpha = C_{so}/C_{sw}$). As expected, whatever $R_k$, the $P_a$ vs $C^0$ curves converge to the limit ($\alpha = C_{so}/C_{sw}$) beyond which a $C^0$ increase can not, obviously, occur. When $C^0$ approaches 0 ($C_w^{eq} \approx 0$), $P_a$ coincides with the partition coefficient $P$ (Martin et al., 1983), and its expression, in terms of model parameters, becomes (Eqs. (21) and (22)):

$$P = \lim_{C^0 \to 0} (P_a) = R_k = \frac{k_{wo}}{k_{ow}} \tag{24}$$

Table 1 shows the $P$ value for the four experimental conditions examined calculated according to Eq. (24). While similar results for the nimesulide water/*n*-octanol partitioning at 37 °C were found by Colombo (1996) ($P_{pH\ 7.5}^{Colombo} = 17.3$), a wide variety of piroxicam water/*n*-octanol partition coefficient values appeared in literature. However, in our opinion, the most reliable value at 25 °C and pH 7.4 is $P = 1.8$ (Wiseman and Lombardino, 1982; Wieseman et al., 1976; Macheras et al., 1990), while Yazdanian (Yazdanian et al., 1998) reports $P = 0.8$ at 37 °C and pH 7.4, these being almost the same conditions used in this work. Although this last datum differs from that reported in Table 1, a proper comparison is not totally correct as our value is determined in the limit $C^0 \approx 0$, and we do not know which were the exact conditions used by Yazdanian. Thus, for a proper comparison, nimesulide and piroxicam partition coefficients were measured at pH 1.2, 37 °C, by means of equilibrium tests as described in the Experimental section. The $P_a$ values determined are:

$$P_a^{nime} = \frac{C_o^{eq}}{C_w^{eq}} = 83.5 \pm 4.6$$

$$P_a^{piro} = \frac{C_o^{eq}}{C_w^{eq}} = 8.4 \pm 0.1$$

Consequently, bearing in mind that from Eq. (21) and Eq. (24) follows:

$$P = R_k = P_a\left(\frac{(C_{sw} - C_w^{eq})\alpha}{C_{so} - C^0(R_v + 1) + C_w^{eq}R_v}\right) \tag{25}$$

we have

$P^{nime} = 79.6$ $\quad$ $P^{piro} = 8.4$

as the correction factor of Eq. (25) is equal to 1.0044 and 0.954 for the piroxicam and nimesulide case, respectively. The good agreement between $P$ values obtained by means of the kinetics (Table 1) and equilibrium measurements further confirms the reliability of the new proposed kinetics model. This is of paramount importance since allows the determination of the rate constants $k_{ow}$ and $k_{wo}$ resorting to experimental data referred to the aqueous phase only, thus avoiding the much more complex drug determination in the oil phase. Indeed, as the model well describes both the kinetics and the equilibrium characteristics of the experimental data, the oil drug concentration predicted by the model has to be correct as a mass balance is used for its determination (Eq. (2)).

The calculation of $P$ by means of Eq. (7) fitting on kinetics data leads to $P^{piro} = 8.7$ and $P^{nime} = 66.5$. It is evident that for the nimesulide case the estimation of $P$ differs from that previously experimentally measured and calculated according to our model (fitting on kinetics data). This is not surprising in the light of the very low nimesulide water solubility. This, again, underlines the unsuitability of Eq. (7) when $C^0$ does not tend to zero (this condition is, de facto, met in the piroxicam case, but not in the nimesulide case).

## 5. Conclusions

In this work we propose a new mathematical model describing and predicting the oil–water partitioning with particular reference to sparingly water-soluble drugs. The suitability of the model is proved by both the very good data fitting and the good agreement between the value of the partition coefficient measured by means of an equilibrium approach and that deriving from the kinetics model. Thus, the model proposes a reliable tool to match the problem of drug partitioning even in the case of sparingly soluble drugs in one or both the polar and apolar phase. Additionally, as a consequence of the theoretical approach developed, we suggest a simple way for correcting the experimentally determined apparent partition coefficient (Eq. (25)).

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