International Journal of Pharmaceutics, 94 (1993) 23–30

IJP 03059

An application of regular solution theory in the study of the solubility of naproxen in some solvents used in topical preparations

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(Received 23 June 1992)
(Modified version received 29 September 1992)
(Accepted 30 September 1992)

Key words: Naproxen; Solubility; Regular solution; Topical preparation

Summary

The solubility of naproxen was studied in different solvents in order to test the possible application of the theory of regular solutions in preformulation studies of a pharmaceutical form for dermatological application. The solvents tested were (I): dibutyl adipate, di(2-ethylhexyl) adipate, oleyl alcohol, propylene glycol dipelargonate, isopropyl myristate, 2-octyldodecanol, decyl oleate, oleyl oleate and isopropyl palmitate. These solvents are normally used in the production of this type of pharmaceutical form and are characterised by their low polarity. Naproxen was also tested in the mixtures (II) of these solvents with others of higher polarity (ethyl and isopropyl alcohol) in proportions such that, according to the theory, the parameter of the mixture equals that of the solute. It was found that, despite the low polarity of the initial solvents (I), naproxen only seems to form regular solutions with some of them (di(2-ethylhexyl) adipate, 2-octyldodecanol and oleyl alcohol), whereas in the others both negative and positive deviations were observed as regards the solubility values predicted by the theory. These deviations may be due to the chameleonic characteristics of the solute, inducing different solute-solute or solute-solvent interactions, depending on the polarity of the solvent. This may also explain the diverse, substantial increases in solubility of naproxen in the different mixtures (II).

Introduction

As absorption through the skin occurs by a process of passive diffusion (Idson, 1975; Barry, 1983) many researchers have shown that it can be verified more rapidly when, for a fixed quantity of active substance, this is in saturated solution (Ostrenga et al., 1971a,b; Zuber et al., 1982; Catz and Friend, 1990), which mainly depends on the choice of solvent. The complexity of topical pharmaceutical forms and the arbitrary selection, in most cases, of the components of the excipient hinders a priori understanding of the type of dispersion caused when excipient and drug are mixed, with the result of frequent differences in the efficacy of the drug (Dempski et al., 1969; Ashton et al., 1988).

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Adequate selection would be simplified by application of a method which allowed us to know at least approximately which excipients guarantee the solubility of the active substance.

Perhaps the simplest of all present theories on the dissolution process is that based on the concept of regular solution. Taking as reference the state of supercooled liquid solute, Hildebrand et al. (1970) expressed solubility of a solute in a liquid with which it constitutes a regular solution as:

$$-\ln X_2 = -\ln X_2^{ideal} + \frac{V_2\phi_1^2}{RT}(\delta_2 - \delta_1)^2 \qquad (1)$$

where X_2 expresses solubility and X_2^{ideal} represents ideal solubility of the drug at temperature T (in K), V_2 is the molar volume of the solute, ϕ_1 denotes the fraction of volume of the solvent and δ_2 and δ_1 are the parameters of total, absolute or Hildebrand solubility of the solute and the solvent, respectively.

As Restaino and Martin (1964) showed, the above equation is strictly applicable to non-polar systems. It also adjusts to the solubility of semipolar solutes in not especially polar solvents, when the molar volumes of both are comparable (Bowen and James, 1970). This technique has been successfully used to predict, for example, the solubility of hydrocortisone in non-polar solvents (Hagen and Flynn, 1983), griseofulvin in glycerides (Grant and Abougela, 1984) and different steroids in the homologous series of *n*-alkanes and *n*-alcohols (C_5–C_{12}) (Gharavi et al., 1983).

On the basis of the Scatchard-Hildebrand equation, Adjei et al. (1980) and Martin et al. (1980, 1981a, 1982a,b) developed different relationships, in some of which (Martin et al., 1981b, 1989) the partial parameters of Hansen (1967) intervene (dispersion, polar and hydrogen bonding) in order both to predict the solubility and also to explain the deviations observed as regards Eqn 1 in the solutions of semi-polar and polar solutes in solvents of variable polarity.

Henceforth, we shall refer to the solubility parameter as (δ), and the Hansen parameters as those of dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h). Any one of these is expressed in $cal^{1/2}\ cm^{-3/2}$, which equals 2.0455 $MPa^{1/2}$ (Barton, 1975).

This paper sets out to apply the theory of regular solutions to the selection of solvents, which are the major components of a topical 5% (w/w) preparation of naproxen. This is a substance of demonstrated anti-inflammatory properties when applied in this proportion and in this manner (Chowhan and Pritchard, 1978). We also propose to ascertain whether this theory allows prediction of the drug's solubility in what are generally classified as low polarity solvents.

Solvent selection

Because of their therapeutic applications, solvents must fulfil a number of conditions, such as:

TABLE 1

Some characteristics of the selected solvents

	MW_1	V_1	δ_1	δ_d	δ_p	δ_h
Isopropyl myristate	270.46	310.7	8.53	7.92	0.80	1.99
Isopropyl palmitate	298.52	342.9	8.54	7.99	0.72	1.90
Oleyl oleate	523.95	605.9	8.60	8.30	0.41	1.43
Decyl oleate	422.75	482.3	8.61	8.22	0.51	1.60
Di(2-ethylhexyl) adipate	370.50	393.4	8.91	7.97	0.89	2.51
2-Octyldodecanol	298.56	352.7	9.01	7.88	0.70	3.63
Oleyl alcohol	268.49	315.0	9.10	8.13	0.79	3.84
Propylene glycol dipelargonate	356.55	377.0	8.99	8.02	0.93	2.56
Dibutyl adipate	258.34	264.6	9.26	7.87	1.33	3.06

MW_1, molecular weight; V_1, molar volume ($cm^3\ mol^{-1}$) and δ_1 ($cal^{1/2}\ cm^{-3/2}$) according to Fedors (1974); δ_d ($cal^{1/2}\ cm^{-3/2}$) according to the homomorph concept (Fedors, 1974); δ_p and δ_h ($cal^{1/2}\ cm^{-3/2}$) according to Hansen and Beerbower (Barton, 1983; pp. 85–86).

they must be commonly used in the preparation of systems meant for topical use; they must be liquid substances of low vapour pressure at room temperature; their solubility parameters must be as similar as possible to that of the active substance. Thus according to the theory of regular solutions, solution of the drug in the excipient is improved. After consulting several texts (Robert and Glas, 1982; Barry, 1983; Flick, 1989) we made an initial selection of the substances meeting the first two of the aforementioned conditions and which are generally defined as 'liquid, oily components, with emollient and dissolving properties of the usual components in preparations of topical use'.

As the solubility parameter values of these substances were not provided by the bibliography, we determined them by the method of contribution of groups of Fedors (1974). We then selected those solvents (Table 1) which presented values for the solubility parameter close to that of naproxen (9.7 $cal^{1/2}$ $cm^{-3/2}$; Contreras et al., 1992).

Materials and Methods

Materials

Naproxen (D-2-(6-methoxy-2-naphthyl)propionic acid) was acquired from Elmu S.A. Its fusion temperature, infrared spectrum and optical rotation agreed with the values included in USP XXII and BP (1988). Glyco Ibérica provided isopropyl myristate, propylene glycol dipelargonate (Glyco PR-827) and isopropyl palmitate (Glyco I-309); Henkel supplied oleyl oleate (Cetiol), decyl oleate (Cetiol V), 2-octyldodecanol (Eutanol G), oleyl alcohol (Eutanol H-D) and dibutyl adipate (Cetiol B); and Aldabo-Julia supplied di(2-ethylhexyl) adipate (Cromadol DOA). All of these are defined by the different companies as technical products for cosmetic use. They were used as received.

Methods

Determination of the experimental solubility of naproxen

Of all the methods used to determine the solubility of a solid in a liquid, we have chosen that based on the determination of the quantity of solute present in a saturated solution, in equilibrium with the solid solute. This method is widely used by, among others, Martin et al. (1980). The methodology was described in a previous paper (Contreras et al., 1992). In order to reduce the total saturation time of the samples tested we have modified the preparation technique by adding the active substance to the solvent at 35°C until a precipitate appeared. The samples sealed with silicone were then mechanically shaken at 25°C, after which the test continued as described in the aforementioned paper.

The saturated solutions diluted with ethanol or isopropyl alcohol were analysed by spectrophotometry (Perkin Elmer, 124 model) at the maximum absorption wavelengths of naproxen, in which the non-polar solvent does not interfere (271 or 316 nm).

In any case, and for each of the weights of the samples analysed, we deduced the quantity of solute and solvent present in g and mol (molecular weight of naproxen, 230.3), the solubility being later expressed in molar fraction and percent (w/w).

Determination of the solubility of naproxen according to the theory of regular solutions

This determination was carried out by applying Eqn 1, in which the first term (X_2^{ideal}) is obtained from the equation proposed by Hollenbeck (1980):

$$-\log X_2^{ideal} = \frac{\Delta S_F}{R}\left(\log \frac{T_F}{T}\right)$$

where ΔS_F is the entropy of the solid at the fusion point (T_F) and equal to $\Delta H_F/T_F$. The molar heat of fusion (ΔH_F) of naproxen at the point of fusion ($T_F = 439$ K) was determined by calorimetric techniques, by DSC (Mettler TA 2000), obtaining $\Delta H_F = 164.2$ J $g^{-1} = 7030.06$ cal mol^{-1} and $\Delta S_F = 21.0047$ cal mol^{-1} K^{-1} (Con-

treras et al., 1992). Therefore, $X_2^{ideal} = 2.12 \times 10^{-2}$ at the temperature of the experiment (298.5 K).

The second term corresponds to the coefficient activity value of the solute in the solution as regards that of the supercooled liquid solute. Determination was carried out by taking unity as the solvent fraction (ϕ_1), the values previously obtained (Contreras et al., 1992) as molar volume ($V_2 = 177$ cm^3 mol^{-1}) and solubility parameter ($\delta_2 = 9.7$ cal$^{1/2}$ cm$^{-3/2}$) of naproxen, and the value obtained by the group contribution method of Fedors (1974) (Table 1) as the solubility parameter of the solvent (δ_1).

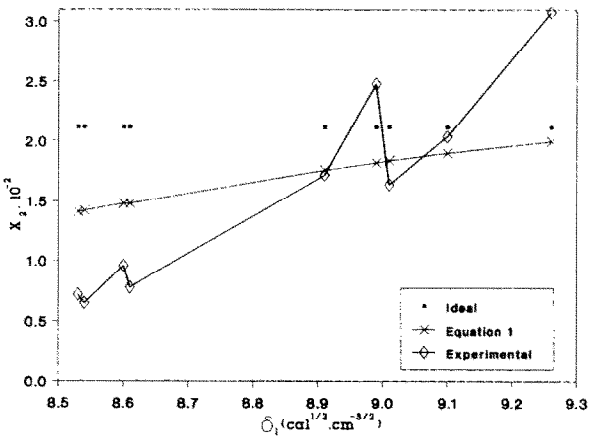

Fig. 1. Solubility of naproxen, according to the solubility parameter of the solvent.

Results and Discussion

The solubility of the naproxen in all the solvents with which it forms ideal solutions equals 2.12×10^{-2}, expressed as a molar fraction, and at 298.5 K, as deduced above. These solutions are characterised by zero molar solution enthalpy and entropy, i.e., there is neither modification of the molar volume, nor interactions between the components and the molecules are arbitrarily distributed.

However, when naproxen makes up regular solutions, these are characterised by a molar solution enthalpy equal to the ideal (zero), but the entropy is different from this value as a consequence of the interactions caused by dispersion forces between the solute-solute, solute-solvent and solvent-solvent molecules (Hildebrand et al., 1970). Quantitatively, the solubility of naproxen in these solutions depends on the solubility parameter of the solvent (Eqn 1), increasing when the solubility parameter of the solvent approaches that of the solute ($\delta_2 = 9.7$ cal$^{1/2}$ cm$^{-3/2}$) (Fig. 1). It would reach a maximum value coincident with its ideal solubility when the solubility parameters of the solute and solvent are similar.

The low polarity of the selected solvents suggests the possibility of obtaining regular solutions when naproxen is dissolved in them. On comparing their experimental solubility with the theoretical value obtained by application of the Scatchard-Hildebrand equation (Fig. 1), we observe some discrepancies between the two values, which reveal that not all the solutions examined are strictly regular, and therefore the interactive forces established between the different molecules are not exclusively dispersive.

These liquids present ester or alcohol functions. According to the classification by Pimmentel and McClellan (Barton, 1983), the former has the capacity to accept and the latter to accept and donate protons. The naproxen molecule has greater polarity and a greater capacity to form hydrogen bonds than these liquids ($\delta_d = 9.40$; $\delta_p = 1.67$; $\delta_h = 6.68$ cal$^{1/2}$ cm$^{-3/2}$) (Contreras et al., 1992), as it includes two functional groups (ether and aromatic ring) capable of accepting protons, and another carboxylic group which can accept or donate them, depending on the nature of the solvent. According to Nelson et al. (1970), the solubilities of solutes with similar characteristics to those of naproxen can present positive or negative deviations as regards the theoretically deduced values, due to the strong influence of the partial mixture on the heat of the total mixture, as a consequence of the specific interactions established between solute and solvent.

In all the solvent with the lowest solubility parameters (isopropyl palmitate and myristate, oleyl oleate and decyl oleate) and high dispersion parameters, low polarity and low capacity for formation of hydrogen bonding (Table 1), the

solubility of naproxen is practically half of that deduced theoretically (Fig. 1). This anomaly can only be explained by the probable auto-association of naproxen molecules, forming dimers or higher species, which neutralise their own polarity, and with different solubility properties from those of the monomer form, resulting in a considerable decrease in their solubility. A similar phenomenon was observed by Martin et al. (1985) in molecules with acid characteristics similar to those of naproxen.

In comparison with the aforementioned liquid substances, di(2-ethylhexyl) adipate, 2-octyldodecanol and oleyl alcohol present solubility parameters slightly closer to that of naproxen, similar polarities and a higher capacity for formation of hydrogen bonding (Table 1). The experimental solubility of naproxen in these substances is very similar to that deduced theoretically (Fig. 1), especially in di(2-ethylhexyl) adipate, where both values coincide. The drug seems to form regular solutions with these solvents.

The solubility of naproxen in dibutyl adipate and in propylene glycol dipelargonate is greater than that predicted by Eqn 1 and also the ideal solubility (Fig. 1). This suggests the establishment of negative interactions between the molecules of solute and solvent, which may be due to the increase in polarity of both liquids (which include two groups of esters in their molecules) in comparison with all those considered previously. Moreover, their solubility parameters are close to that of naproxen, although the capacity for formation of hydrogen bonding is average for those tested (the alcohols have higher capacity). Concerning the increase in solubility, a number of factors seem to be involved: proximity of the solubility parameter, increase in polarity and capacity for formation of hydrogen bonding.

The study of the solubility of naproxen in the selected solvents considered to be of low polarity reveals a pattern of behaviour similar to that of the molecules described as 'chameleonic' by Hoy (1970), i.e., which have a capacity to adapt to their medium. In very low polarity liquids naproxen exposes its least polar surface, thus considerably reducing its solubility. However, its solubility increases noticeably with polar solvents, due to its high capacity for specific interaction.

Solubility in mixtures

The absolute solubility of naproxen in each of the selected liquids is never more than 2.8% w/w (Fig. 2). Given the influence that the specific interactions between solute and solvent have on its solubility, and given that our aim is to design systems in which the drug will be in solution at 5% w/w concentration, we must attempt to in-

TABLE 2

Correlation between the increase in solubility of naproxen and the amount of alcohol added to the solvent of least polarity, both expressed in % (w/w)

	Ethanol		Isopropanol	
	% ethanol	% Δsolb.	% isopropanol	% Δsolb.
Dibutyl adipate	10.2	165.8	14.0	163.7
Oleyl alcohol	15.3	69.0	20.8	58.5
Propylene glycol dipelargonate	16.5	255.4	22.4	269.3
2-Octyldodecanol	17.3	109.0	23.4	88.4
Di(2-ethylhexyl) adipate	17.9	463.0	24.1	427.3
Oleyl oleate	–	–	30.0	785.7
Decyl oleate	–	–	32.1	838.6
Isopropyl myristate	25.0	816.0	32.9	766.7
Isopropyl palmitate	26.0	881.0	34.6	877.6
	$N = 7$ $r = 0.89015$ $P(< 0.01)$		$N = 9$ $r = 0.89512$ $P(< 0.01)$	

crease the solubility of the active substance by using mixtures of the different solvents tested. We therefore use the theory of regular solutions, which establishes that maximum solubility is obtained when solute and solvent present the same solubility parameter value, and, moreover, that in a mixture of two liquids with different parameters, one higher and one lower than that of the solute, solubility in the mixture increases as regards the individual solvents (Barton, 1975).

Each of the initial liquids considered to be of low polarity is mixed with others of higher polarity, which are acceptable in dermatological preparations. These polar liquids must have a solubility parameter which permits their dilution with those previously selected and with naproxen. According to the criterion proposed by Barton (1975), they must fulfil the following conditions:

$$|\delta_1 - \delta_2| \leq 2.5 \text{ cal}^{1/2} \text{ cm}^{-3/2} \geq |\delta_3 - \delta_2|$$

respectively, Subscripts 1 and 3 represent the solvents which are more and less polar, than the solute (subscript 2).

Of the possible solvents which fulfilled the conditions established above, we selected isopropyl alcohol ($\delta_l = 11.5$; $\delta_d = 7.7$; $\delta_p = 3$; $\delta_h = 8$ $\text{cal}^{1/2}$ $\text{cm}^{-3/2}$; $V = 78.6$ cm^3 mol^{-1} (Barton, 1975)) and ethanol ($\delta_l = 12.7$; $\delta_d = 7.7$; $\delta_p = 4.3$; $\delta_h = 9.5$ $\text{cal}^{1/2}$ $\text{cm}^{-3/2}$; $V = 58.5$ cm^3 mol^{-1} (Barton, 1975)), in which the solubility of naproxen is 4 and 7% (w/w), respectively (Contreras et al., 1992).

Since the solubility parameter is an additive property, the mixture of both groups of solvents (low polarity and polar solvents) must be made in adequate proportions, so that the resulting mixture has a total solubility parameter value equal to that of the drug (9.7 $\text{cal}^{1/2}$ $\text{cm}^{-3/2}$) (Table 2). The considerable difference in the molar volumes of both groups of solvents makes it advisable to use the formula proposed by Barton (1983):

$$\delta_{1,2} = \left(\frac{X_1}{mX_2 + X_1}\right)\delta_1 + \left(\frac{mX_2}{mX_2 + X_1}\right)\delta_2$$

where X is the molar fraction, δ denotes the solubility parameter, m is the ratio of molar volumes and subscripts 1 and 2 represent the solvents.

Chemically pure ethanol and isopropanol (Quimon) were used. The solubility studies of naproxen in each mixture tested were carried out a 25°C, following the method described above, as too was the evaluation of the different samples.

Experimental Results and Discussion

We deduce from the analysis of the results obtained (Fig. 2) that between both groups of samples (mixtures with ethanol and mixtures with isopropanol) the solubility of naproxen is practically independent of the alcohol used as diluent, i.e. comparable values were obtained between the

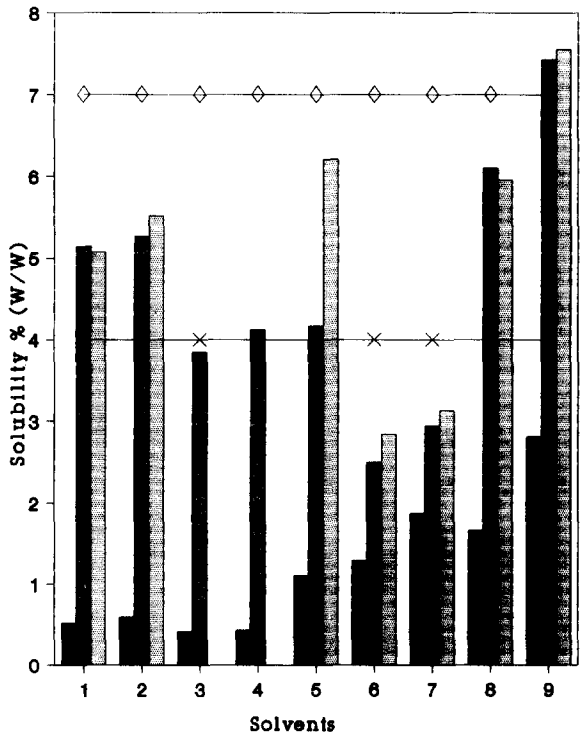

Fig. 2. Solubility of naproxen in ethanol (◇), in isopropanol (×), in low polarity solvents (■) and in the mixture of these with isopropyl (hatched bars) or ethyl alcohol (stippled bars). Low polarity solvent: 1, isopropyl palmitate; 2, isopropyl myristate; 3, oleyl oleate; 4, decyl oleate; 5, di(2-ethylhexyl) adipate; 6, 2-octyldodecanol; 7, oleyl alcohol; 8, propylene glycol dipelargonate; 9, dibutyl adipate.

mixtures in which the solvent of lower polarity coincided. Fig. 2 also shows a large increase in the solubility of naproxen in all the mixtures in comparison to that presented in each of the low polarity liquids used at first. This increase may be due to the concurrence of two factors: the similarity of the solubility parameter of the mixture with that of the solute and the greater capacity for specific interactions.

Nonetheless, these increases are irregular. The alcoholic mixtures of oleyl oleate, decyl oleate and isopropyl palmitate and myristate cause a change in the solubility of naproxen from 0.6% (w/w) when they intervene as isolated components, to 4 or 5% (w/w) in mixtures. The incorporation of either ethyl or isopropyl alcohol in proportions less than 30% seems to overcome the initially adverse conditions, preventing the autoassociation of naproxen molecules and favouring the specific interactions between the different mixtures and the drug. The smaller increases are observed in the mixtures of high molecular weight alcohols (oleyl alcohol and 2-octyldodecanol), despite the fact that these are the initial liquid substances with the greatest capacity of all those tested for formation of hydrogen bonds. In the remaining samples (mixtures of di(2-ethylhexyl) adipate, propylene glycol dipelargonate and dibutyl adipate) the absolute solubilities are the highest of all those observed, being between 6 and 7.5% w/w.

These alcohols (both ethylic and isopropylic) appear to behave differently. The solubility of naproxen in pure ethanol (7% w/w) contrasts with that obtained when this alcohol intervenes as diluent (Fig. 2). The solubility of the drug is never greater than this value, except in the mixture with dibutyl adipate. On the other hand, when isopropanol is used, in a high percentage of the mixtures studied, solubilities were obtained which were greater than those observed with the pure solvent (4% w/w).

Both pure ethanol and pure isopropanol present a high capacity for formation of hydrogen bonding, as well as high polarity. The high solubility of naproxen in each of them can be attributed to these factors and also to the special molecular characteristics of the drug. The mixture of either alcohol with a liquid of lower polarity at times reduces the polarity and the initially total capacity for formation of hydrogen bonding, thus reducing the solubility of these drugs, which depends on the specific interactions between them. This phenomenon is particularly apparent in ethanol, and above all when it is used in mixtures of alcohols with high molecular weight. Isopropanol, which is less polar than ethanol, only manifests the phenomenon in some mixtures (oleyl oleate, 2-octyldodecanol and oleyl alcohol), while in the others it conforms to the predictions of the theory of regular solutions, i.e., increased solute solubility in the mixture of two solvents as regards solubility in the individual components.

The increase in solubility of naproxen in each group of mixtures, as regards that found in each low polarity solvent on its own, cannot exclusively be attributed to the percentage of any added alcohol, as deduced from the high linear correlation coefficient obtained between both parameters (% of added alcohol, % increase in solubility). Close examination of Table 2 reveals that, for each group of samples, similar percentages of any one alcohol do not produce similar increases in solubility. This is probably due to the characteristics of the solute and of the solvent molecules involved. Although the theory of regular solutions is only strictly fulfilled in apolar systems, which are uncommon in pharmacy, as most of the solutes (drugs) are normally semipolar or polar and solvents are very variable, it can be an appropriate method in preformulation studies, as application of its basic principles can aid selection of the components of the pharmaceutical preparation.

Of all the mixtures tested, and due to the similarity of the solubilities of naproxen in ethanol and isopropyl alcohol mixtures, we recommend the former by virtue of its lower percentage and toxicity (Handbook of Pharmaceutical Excipients, 1986).

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