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DISSOCIATION CONSTANTS, SOLUBILITIES AND DISSOLUTION RATES OF SOME SELECTED NONSTEROIDAL ANTIINFLAMMATORIES

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ABSTRACT

Dissociation constants, solubilities and dissolution rates have been investigated for 16 nonsteroidal antiinflammatory active compounds which belong to several chemical groups within the small class of acidic drug substances. The antiinflammatories are mostly characterized by a very low aqueous solubility at lower pH-values. The solubilities increase rapidly with pH's higher than the pK_a. The pK_a-values of the investigated compounds range from 3.5 to 6.3 with a mean directed to 4.6 . The dissolution rate determinations of equimolar amounts at pH 7.5 show a great variation from half a minute to 60 minutes for the 50 % level.

INTRODUCTION

Chemical, physico-chemical and physical properties are fundamental and important data of drug substances in the field of drug formulation, drug design and drug develop-

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ment. Because chemical structure of drug substances results in several technological properties with almost unknown dimensions and variability, only those pharmaceutical technologists, who have to work with the drug in order to make and to ensure a recommended and good drug product are engaged in this field. Some of the fundamental data of a pure drug substance in technology are the aqueous solubility, the dissociation constant and the dissolution rate.

Aqueous solubility of a drug substance can depend on pH. The importance of its knowledge is emphazised e.g. by the development of injectable solutions including a possible pH-dependent chemical instability of the drug substance. pH-dependent solubility can further be important in the case of oral dosage formulations considering variable pH-time-profiles in the gastro-intestinal-tract. The low solubility at acidic pH-values can require for some oral dosage forms of antiinflammatories special formulation factors, e.g. alcalyzing ingredients considering the dissociation which influences physico-chemical and possibly kinetic properties of the salts formed [1].

The dissociation of weak acidic and basic substances may be connected with their pH-dependent solubility; dissociation can influence spectrophotometric analysis and the dissociation constant may perhaps quantify several diffusion controlled processes [2].

The dissolution rate of the pure drug substance is directly related to drug dosage form design and development, e.g., the dissolution must be increased or decreased by means of formulation factors depending on the pharmacokinetic effect desired [3]. The importance of the dissolution rate of antiinflammatories is finally proved by the fact, that some of their drug dosage forms are subject to the dissolution test USP XX, e.g. Fenoprofen

Calcium Tablets, Ibuprofen Tablets, Indomethacin Capsules, Phenylbutazone Tablets, Sulindac Tablets, Tolmetin Sodium Capsules [4].

The objectives of the present investigations are bound to some basics of pharmaceutical technology, i.e., the analysis and the effect of chemical, physico-chemical and physical properties facilitate drug dosage form design and development [5]. The three properties investigated give informations to a theoretical kind of view, in particular in programming a flow-through type dissolution model device by analogue computation [6]. These computations and subsequently the dissolution model devices need to be programmed by intrinsic pH-solubility-time profiles of the compounds independent of their technological formulation. An optimization of the program run has to follow for formulated dosage forms [7].

MATERIALS AND METHODS

Drug Substances

The substances have been dried to weight constance and used as they were without assay.

Azapropazone	Siegfried GmbH, Bad Säckingen, FRG
Clofezone	H. Mack Nachf., Illertissen, FRG
Diclofenac Sodium	Ciba-Geigy AG, Wehr/Baden, FRG
Fenbufen	Cyanamid GmbH, Wolfratshausen, FRG
Fenoprofen Calcium	Eli Lilly GmbH, Gießen, FRG
Flufenamic Acid	Parke, Davis & Company, München, FRG
Flurbiprofen	Dr. K. Thomae GmbH, Biberach/Riss, FRG
Ibuprofen	Klinge Pharma GmbH & Co., München, FRG
Indomethacin	Sharpe & Dohme GmbH, München, FRG
Ketoprofen	Rhône-Poulenc Pharma GmbH, Norderstedt, FRG

Naproxen	Grünenthal GmbH, Stolberg, FRG
Niflumic Acid	von Heyden GmbH, München, FRG
Oxyphenbutazone	Ciba-Geigy AG, Wehr/Baden, FRG
Phenylbutazone	Ciba-Geigy AG, Wehr/Baden, FRG
Piroxicam	Pfizer GmbH, Karlsruhe, FRG
Tolmetin Sodium	Cilag-Chemie GmbH, Alsbach, FRG

Buffer Substances

p.a. grade, E. Merck AG, Darmstadt, FRG

Buffer Solutions

Solution A:		Solution B:	
HCl 1M	94.0 ml	$Na_2HPO_4 \cdot 2H_2O$	20.5 g
Glycocoll	0.5 g	KH_2PO_4	2.8 g
NaCl	3.68 g	NaCl	0.15 g
H_2O	to 1000.0 ml	H_2O	to 1000.0 ml

Buffer solutions with selected pH-values have been produced by mixing solution A with solution B to 100.0 ml as shown in figure 1.

Dissociation Constants

Drug solutions were prepared by dissolving an amount of 0.5 to 2.0 mg in 100 ml of both solution A and solution B. Different amounts dissolved depend on the minimum solubility in solution A (acidic) and on an optimum UV-absorption within 0.1 and 0.9 absorption units. Both solutions have been mixed to selected and controlled pH-values according to the mixing diagram (see fig. 1). The solutions were measured spectrophotometrically in a 1 cm-cell between 200 and 400 nm. These measurements are the reference assays for the solubility measurements (see beyond).

Determination of pK_a

Method A for substances having a change in the wavelength of the absorption maximum with pH. An example is given for Niflumic Acid in figure 2 left side.

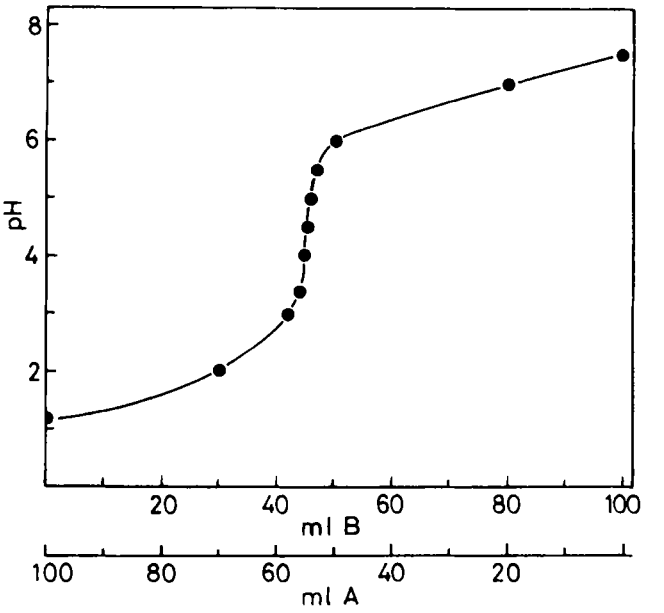


FIGURE 1

Mixing diagram of selected pH-values by buffer solution A and B

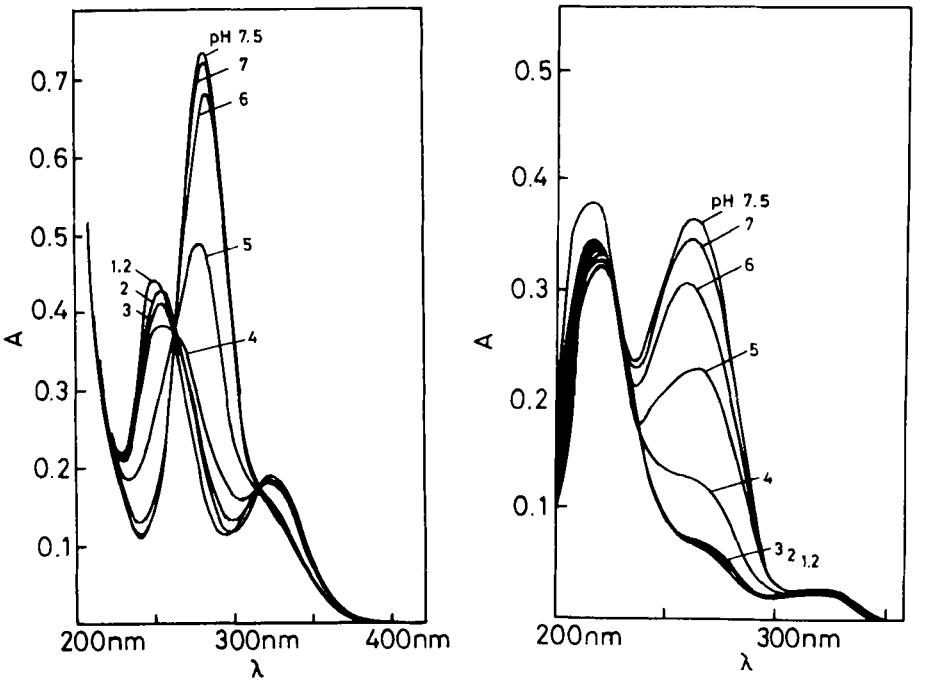


FIGURE 2

Dependence of spectral absorption characteristics of Niflumic Acid (left, used for method A-pK_a-determination) and of Clofezone (right, used for method B-pK_a-determination) on different pH-values in aqueous solution

The wavelength of maximum absorption λ has been plotted vs. pH as shown in the tables. The dissociation constant has been either extrapolated graphically and calculated by determining the maximum change with pH.

Method B for substances showing a change in absorption height at the same wavelength with pH. An example is given for Clofezone in figure 2 right side.
The change in absorption height with pH (dA/dpH) has been differentially plotted as shown in the tables. The dissociation constant has been either extrapolated graphically or calculated by estimation of the maximum change of height with pH. In one case the direct absorption unit-pH-plot for the pK_a-determination is shown.

Solubility

A suitable quantity of the drug substance has been weighed into each buffer solution (100.0 ml). The trials were exposed to a shaking device at room temperature for 48 hours. The dissolved part of the substances was assayed spectrophotometrically at the wavelength of maximum absorption after filtration and suitable dilution.
Protocol for Ibuprofen:

pH	λ_{max} ref. [nm]	λ_{max} test [nm]	ref. abs. (1mg%)	test abs.	amt. exp. [mg]	dil.	solubility [mg%]
7.5	217	217	0.41	0.542	400	1:250	331
7	218	218	0.41	1.0	400	1:100	244
6	217	217	0.393	1.042	400	1: 20	53
5	217	217	0.369	1.078	100	1: 4	12
4	217	216	0.349	1.021	100	-	2.9
3	217	215	0.348	0.815	20	-	2.3
2	216	214	0.361	0.807	20	-	2.2
1.2	215	214	0.392	0.839	20	-	2.1

Each dissolved part was calculated in comparison to the reference assay at the selected pH. Plots of mg% dissolved vs. pH are shown in the tables.
In some cases solubility data enable the determination of dissociation constants as described by Krebs and Speakman [8]. The pK_a-value results in the intercept with the abscissa when plotting $\log(S/S_o - 1)$ vs. pH. The solubility S at any pH is related to the solubility S_o at pH 1.2 . An example for this procedure is given in figure 3 for Phenylbutazone. Further examples are noted in the tables.

Dissolution Rates

Dissolution rates have been determined of equimolar amounts of the pure drug substances ($4.5 \cdot 10^{-5}$ M/900 ml) with apparatus 1 USP XX (rotating basket, 100 rpm). The sieve bottom of the basket was covered inside with a circular filter paper in order to keep the substance within the basket during the test. The dissolution medium used was the buffer solution B (pH 7.5, see above). The amounts dissolved with time have been determined simultaneously by means of a closed tube-pump-circuit. The test procedure has been repeated twice for each drug substance. Plots of % dissolved vs. time are shown in the tables.
In some cases rate constants of dissolution could be estimated from a semilogarithmic plot log % residual vs. time. Examples are given in the tables.

Computer Plots

The computer plotted graphics were arranged by the program "DISSOPLOT3" [9].

Apparatus

Beckman Acta III dual beam spectrophotometer
Zeiss PM 3 mono beam spectrophotometer
Köttermann shaking water bath No. 3047

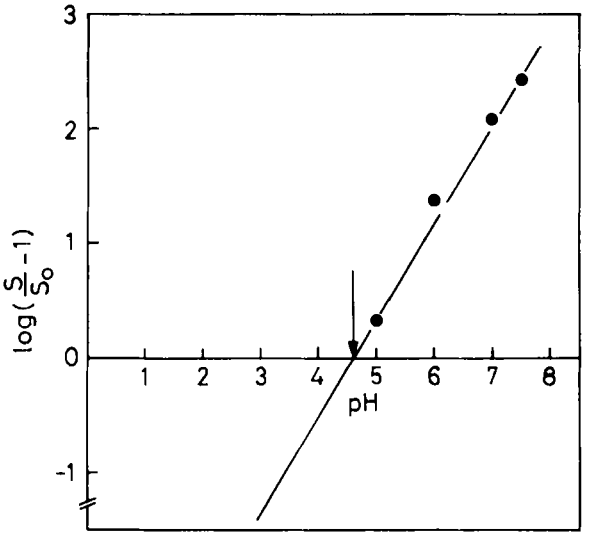


FIGURE 3

Krebs and Speakman-plot for Phenylbutazone (arrow indicates pK_a-value)

Dissolution test apparatus 1 USP XX selfmade according to the USP-requirements

Ismatec mini-micro pump

Commodore CBM 3032, CBM 4040

Watanabe Digiplot WX 4671

RESULTS

The results of the pH-solubility-profiles, dissociation constant determinations and dissolution rate investigations of the nonsteroidal antiinflammatory agents tested are alphabetically summarized in graph-table-combinations. This method allows either to be informed about the values in detail or about tendencies by plots. Each graph-table-combination is engaged in one compound introduced by its name and molecular weight, followed by the graphical pK_a-determination, the pH-solubility-profile and the results of the dissolution rate investigations. Each is finished by comments to the results.

Most of the compounds investigated exhibit pK_a-values between 4.3 and 4.9 . The pK_a's of Azapropazone (6.3), Ibuprofen (5.3) and Piroxicam (5.3) are increased, the pK_a's of Naproxen (4.1), Ketoprofen (3.7) and Tolmetin Sodium (3.5) are decreased in relation to the mean.

The solubility of the substances in acidic media (pH 1.2 to 3.0) do not reach the 10 mg% level. The solubility at pH 7.5 ranges from 31 mg% (Clofezone) to more than 400 mg% (Tolmetin Sodium, Ketoprofen), a half of the substances surpasses the 200 mg% level. Substances with low solubility at pH 7.5 are Azapropazone (73 mg%), Clofezone (31 mg%) and perhaps Niflumic Acid (93 mg%). The rapid increase in solubility at a pH approximately one unit higher than the pK_a is generally admitted to all substances.

The dissolution rates of the substances range from half a minute to about 60 minutes in reaching the 50% level. Nine substances need less than 1 minute to reach this level. Relatively long times have been found for Azapropazone, Clofezone, Oxyphenbutazone and Phenylbutazone. Middle in between Piroxicam and Niflumic Acid are found.

DISCUSSION

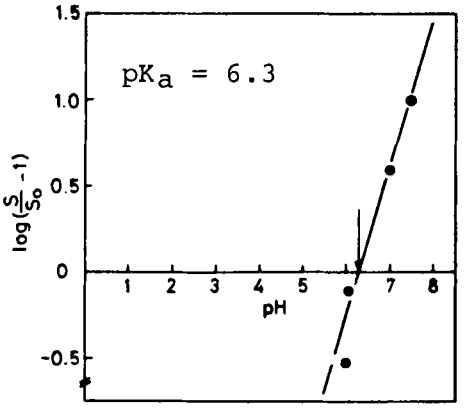
The dissociation constants of the antiinflammatories investigated differ over nearly 3 units, a result, which makes convenient different possible interactions with pharmaceutical ingredients like cationic polymers [10] or cationic parts of antacids [11]. In this matter the more acidic compounds Tolmetin Sodium and Ketoprofen may be of greater interest than the very weak acidic Azapropazone. The sparing solubility in acidic media may turn one to alcalyzing ingredients for a rapid dissolution within the stomach. The better solubility at pH 7.5 has to be reflected upon the normal oral dosage unit and up-

on the rate of disappearance from the GI-tract. The dissolution rates of some substances (Fenoprofen Calcium, Ibuprofen, Indomethacin, Tolmetin Sodium) are intrinsicly so fast, that USP regulations seem to aim at technological processes, but Indomethacin Capsules and Tolmetin Sodium Capsules USP lack any process without the filling. The intrinsic dissolution rates of Azapropazone, Clofezone, Oxyphenbutazone, Niflumic Acid, Flufenamic Acid and Piroxicam are 10 to 100 times lower than those and need attention as well.

COMPOUND

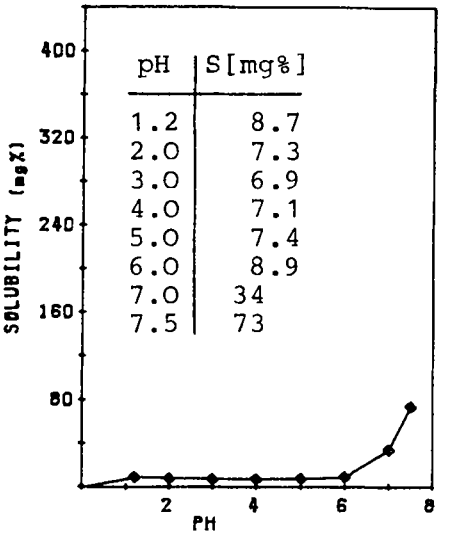
AZAPROPAZONE MW 336.4

DISSOCIATION

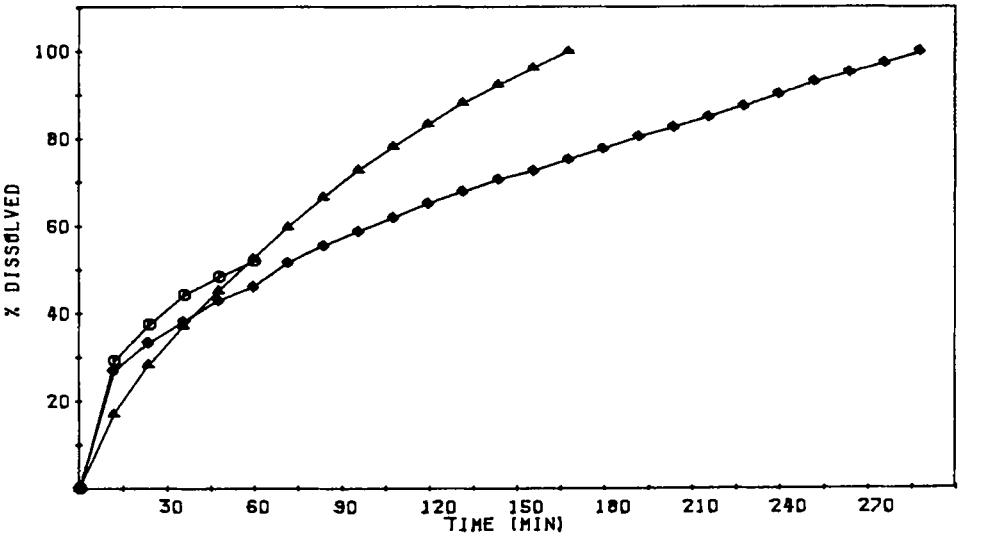


SOLUBILITY

pH	S[mg%]
1.2	8.7
2.0	7.3
3.0	6.9
4.0	7.1
5.0	7.4
6.0	8.9
7.0	34
7.5	73



DISSOLUTION RATE



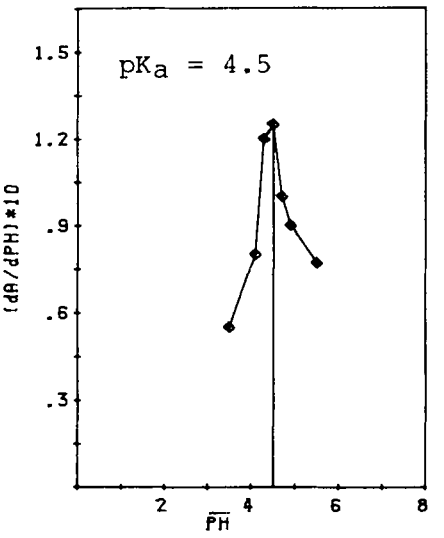
COMMENTS

pKa-determination was only practicable by the solubility procedure, the spectrophotometric methods failed.
Differences 1:10 occured in the solubility within pH 1.2 and 7.5 .
Differences in the dissolution rates depended on the floating of the substance.

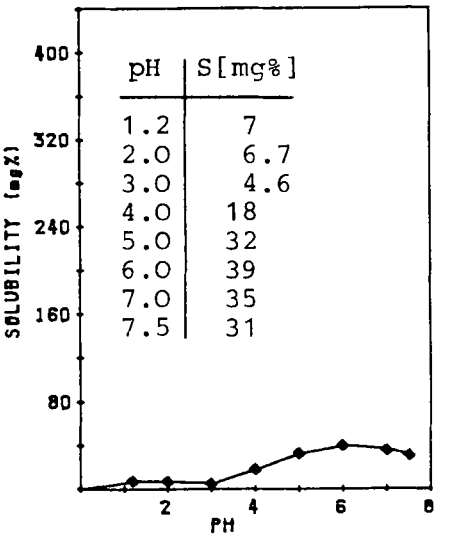
COMPOUND

CLOFEZONE MW 593.1

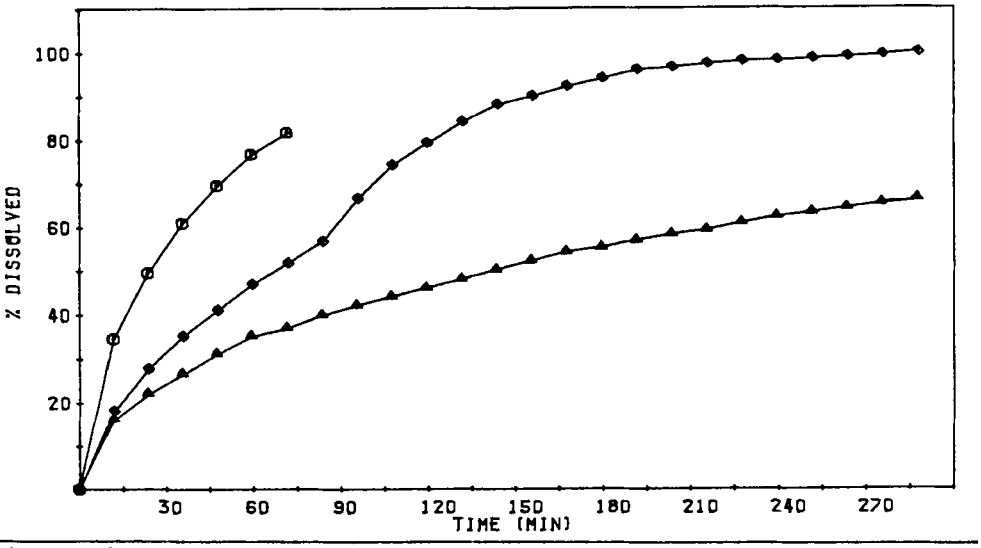
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



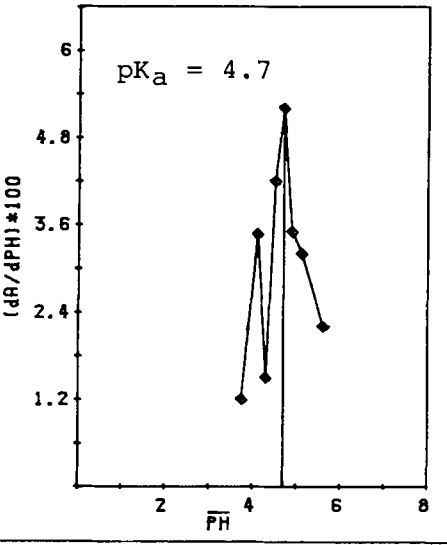
COMMENTS

The pK_a-determination was advantageous to this procedure within the methods proved. Small differences (1:5) in the pH-dependent solubility between pH 1.2 and 7.5 . Floating of the substance results in differences of its dissolution behaviour.

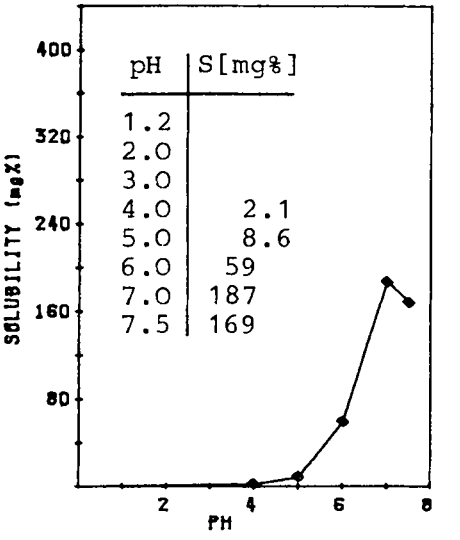
COMPOUND

DICLOFENAC SODIUM MW 318.1

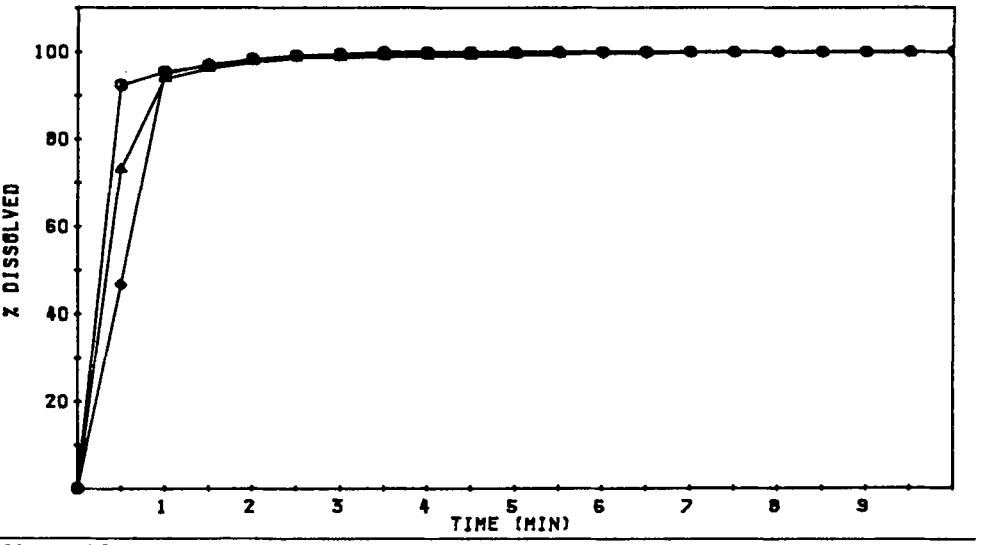
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



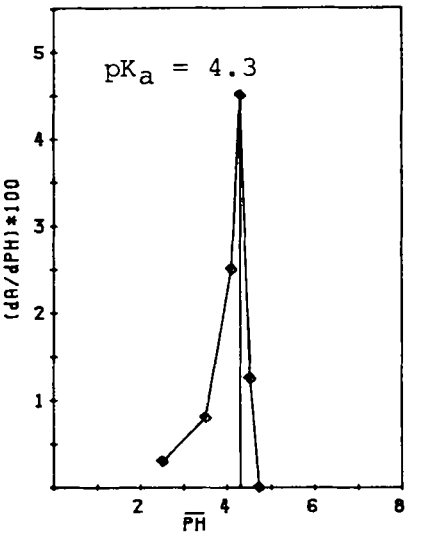
COMMENTS

The exact pK_a-determination should be optimized by another method because of the irregularity at approx. pH 4. The solubilities at pH 1.2 to 3 are below 0.4 mg% (not measurable as indicated).
Uniformity of 3 dissolution rate determinations.

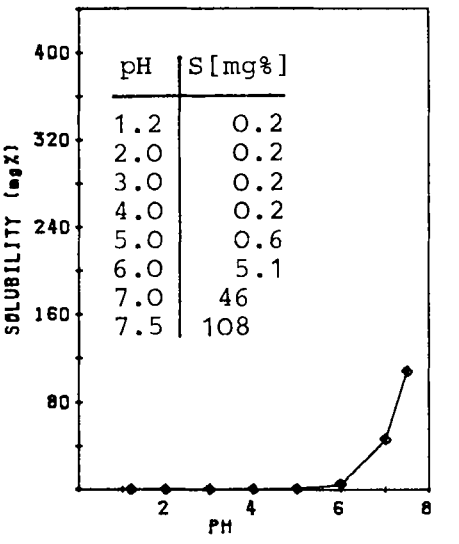
COMPOUND

FENBUFEN MW 254.3

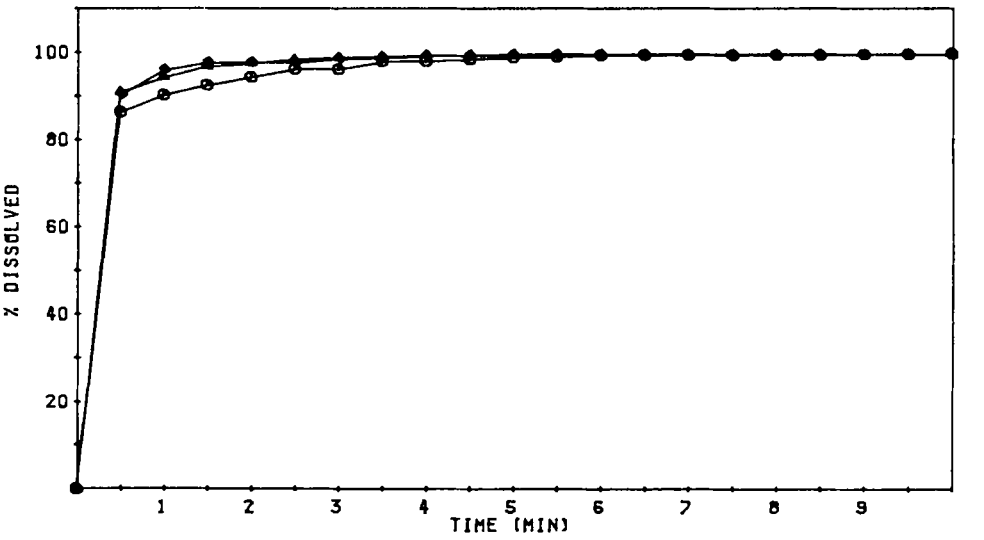
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



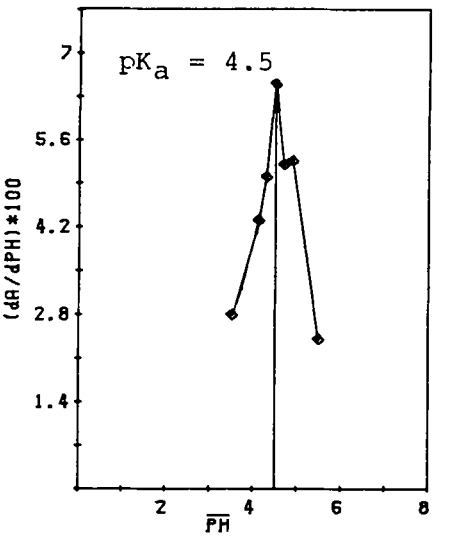
COMMENTS

Standard test concentration is decreased to 0.2 mg% because of the high absorption coefficient. Noticeable solubility begins at pH 6. The dissolution rate determinations require 2 to 4 min to maximum.

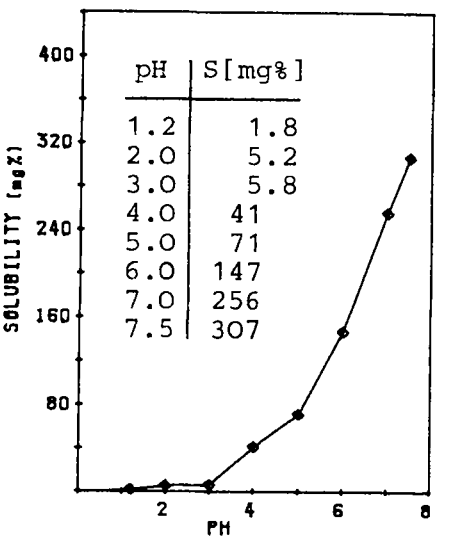
COMPOUND

FENOPROFEN CALCIUM MW 558.6

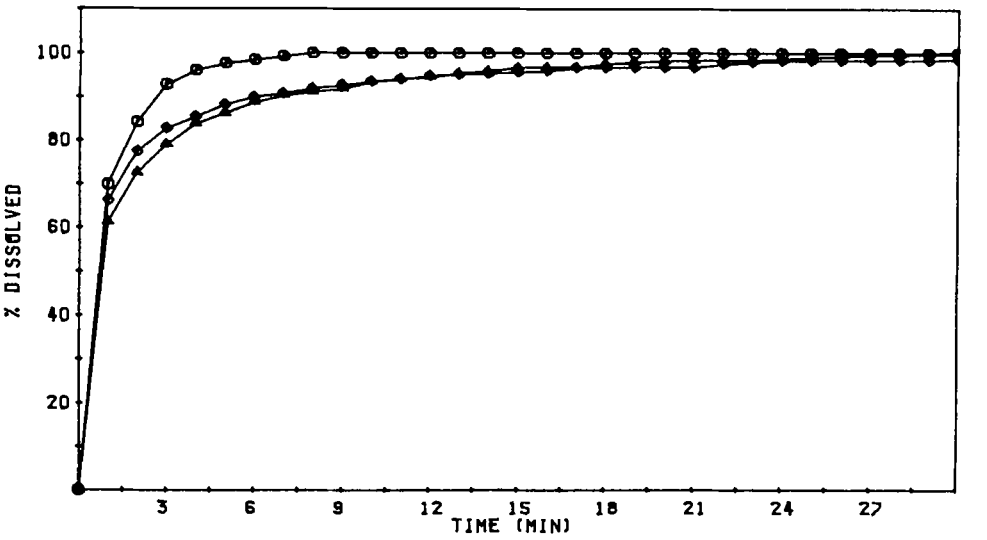
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



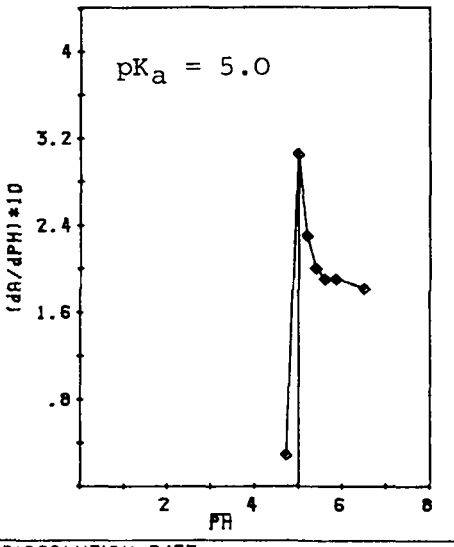
COMMENTS

pK_a-determination was advantageous to this procedure within the methods proved. A perceiving solubility arises at pH 4. It takes 5 to 15 min to reach nearly 100 % of dissolved amount of the drug.

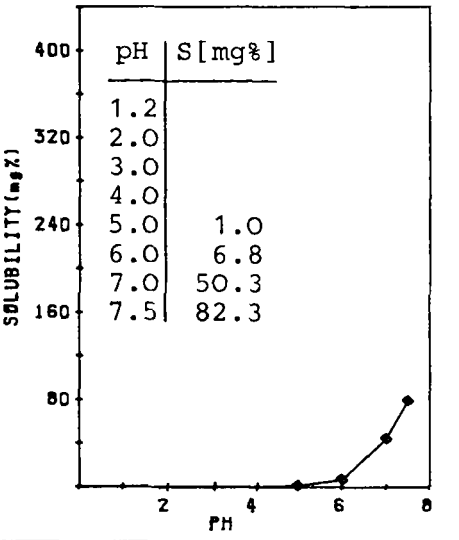
COMPOUND

FLUFENAMIC ACID MW 281.2

DISSOCIATION



SOLUBILITY



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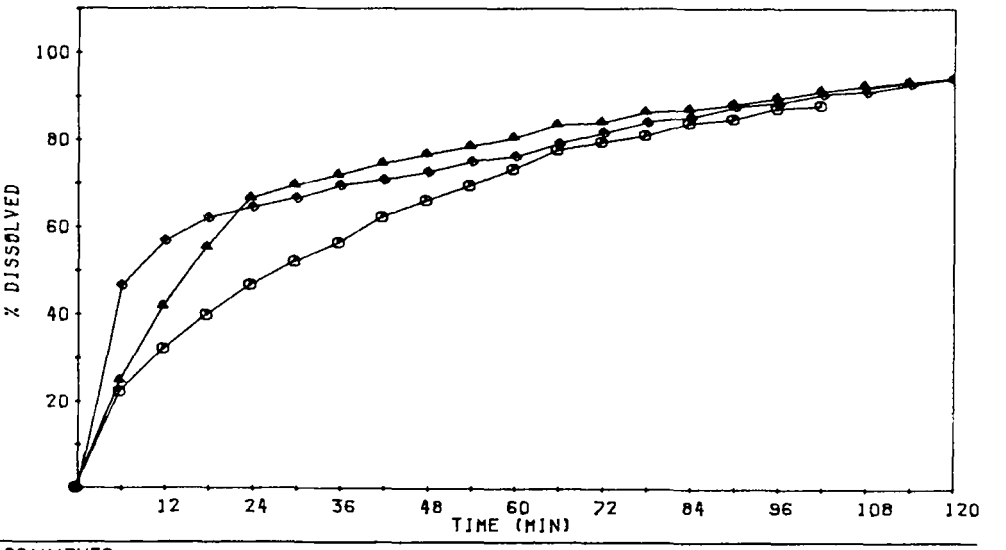


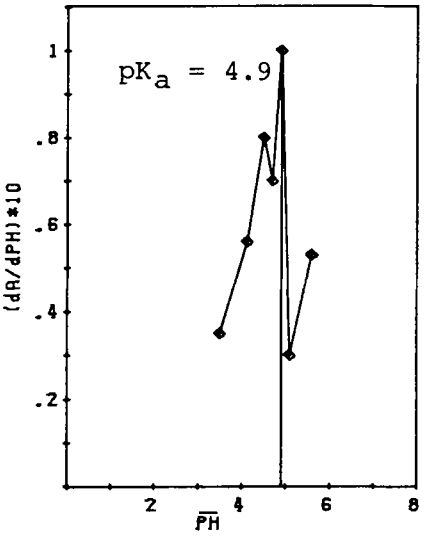
COMMENTS

The pK_a-determination supports only the region of the possible value. The pH-dependent solubility is very low. The 60%-level of the dissolution rate occurs after 20 to 40 min.

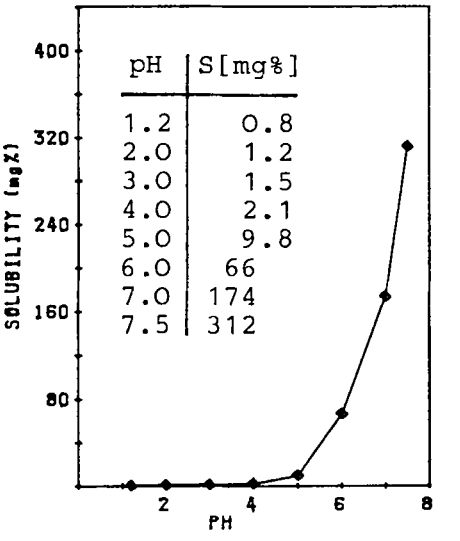
COMPOUND

FLURBIPROFEN MW 244.3

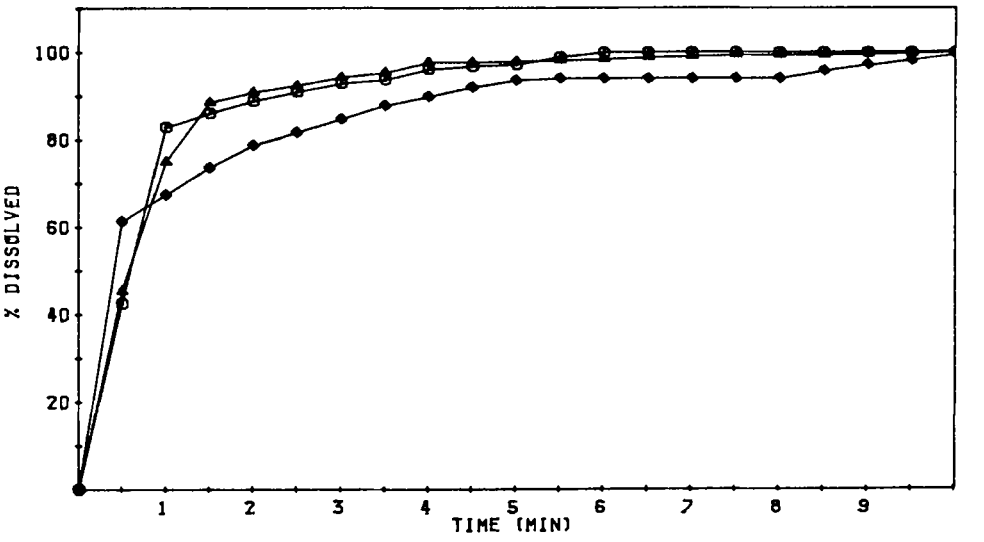
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



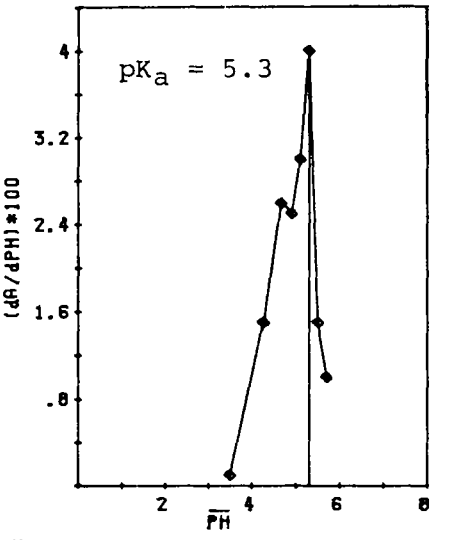
COMMENTS

Other methods for pK$_a$-determination are less evident within these investigations. pH-dependent solubility increases to relatively high amounts. The dissolution rate determinations result in 100 % within 10 min and 80 % within 1 to 3 min.

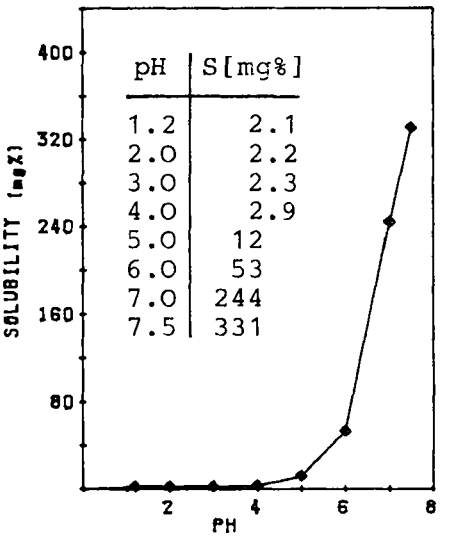
COMPOUND

IBUPROFEN MW 206.3

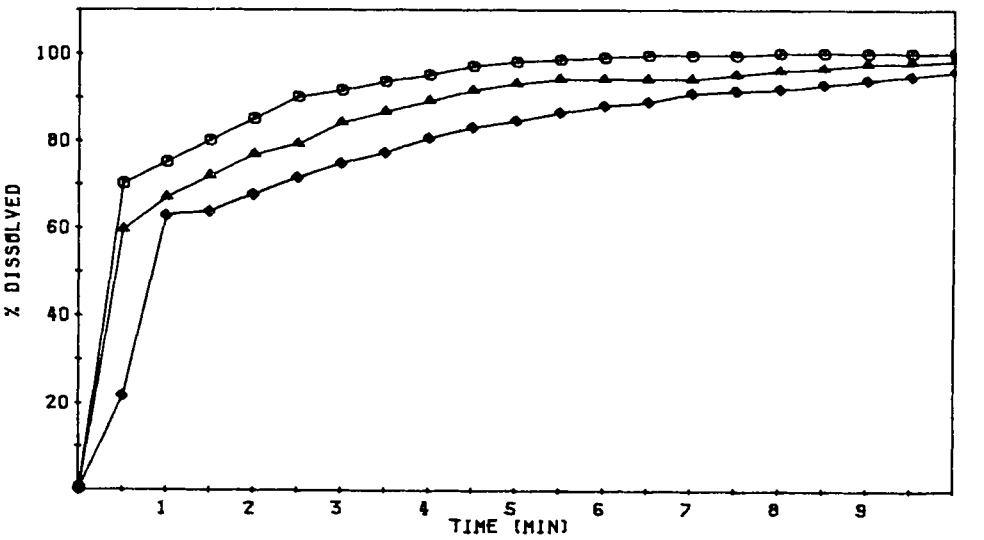
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



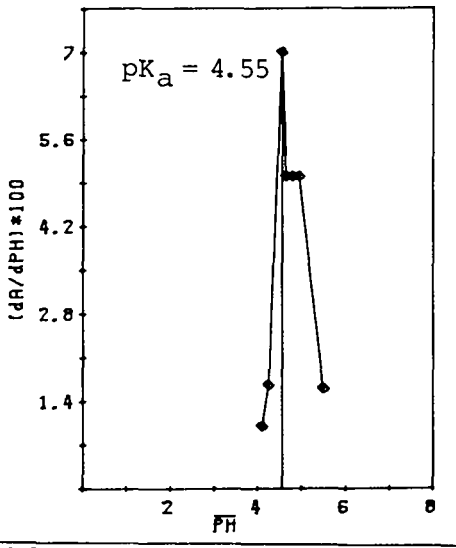
COMMENTS

pK_a-determination is more evident by this procedure than by other methods (lit. data: 5.2 [12]). pH-dependent solubility increases to relatively high amounts.
Rapid dissolution rate.

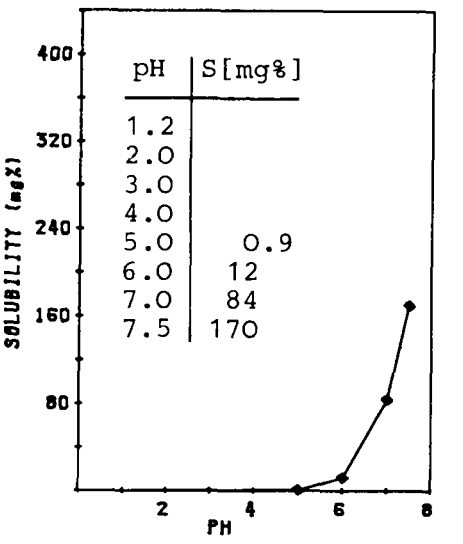
COMPOUND

INDOMETHACIN MW 357.8

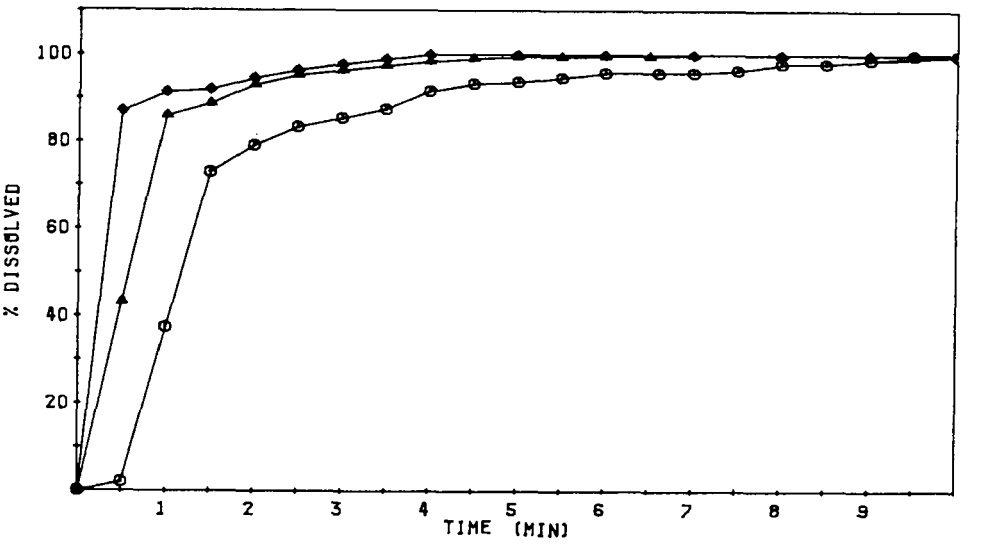
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



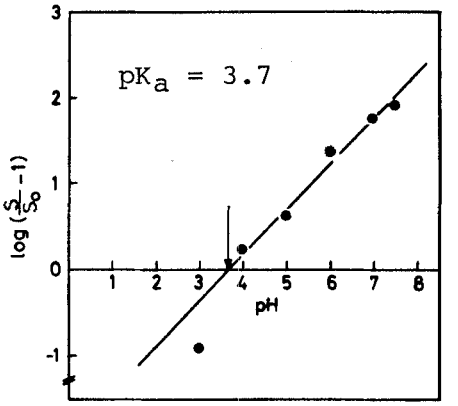
COMMENTS

Rapid change of absorption with change in pH. Lit. data pK_a = 4.5 [13]. The solubility up to pH 4 is below 0.9 mg%. Rapid dissolution rate.

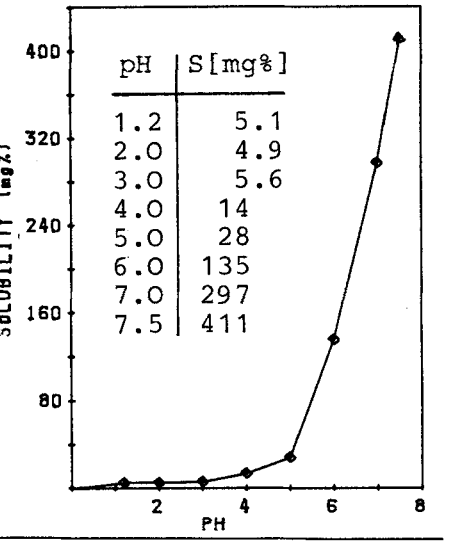
COMPOUND

KETOPROFEN MW 254.3

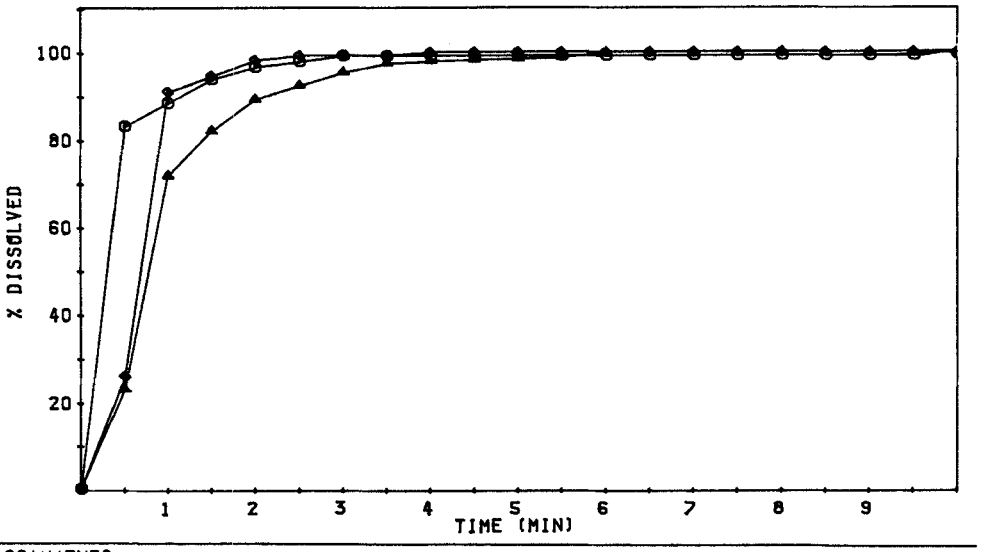
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



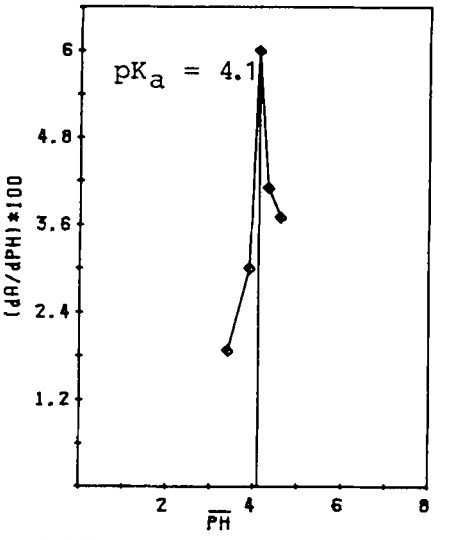
COMMENTS

pK_a-determination was only practicable by the solubility procedure. The solubility at pH 7.5 is higher than 400 mg%. The dissolution rates require 1 to 3 min to reach the maximum.

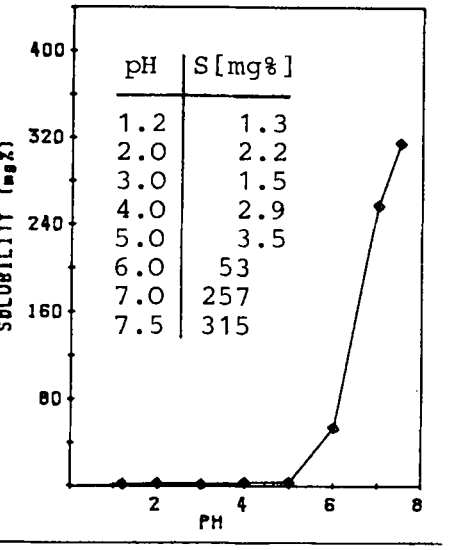
COMPOUND

NAPROXEN MW 230.3

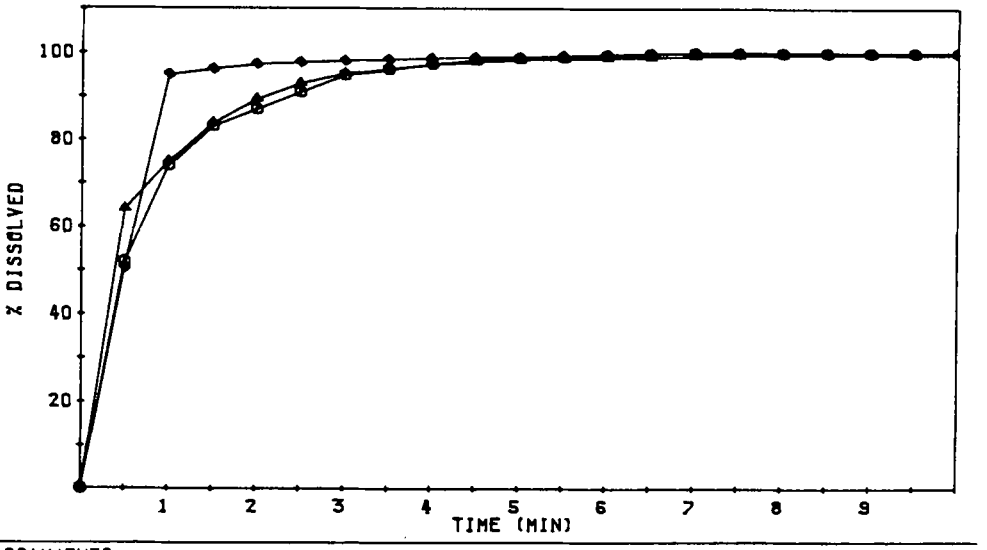
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



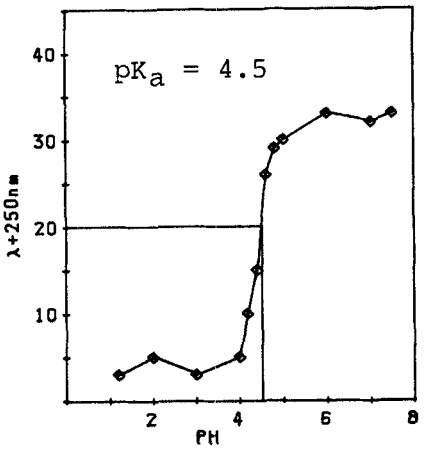
COMMENTS

The standard test solution is 0.2 mg% because of the high absorption coefficient. The solubility increases very rapid at pH 6 and higher. It takes 5 min or less to reach 100 %.

COMPOUND

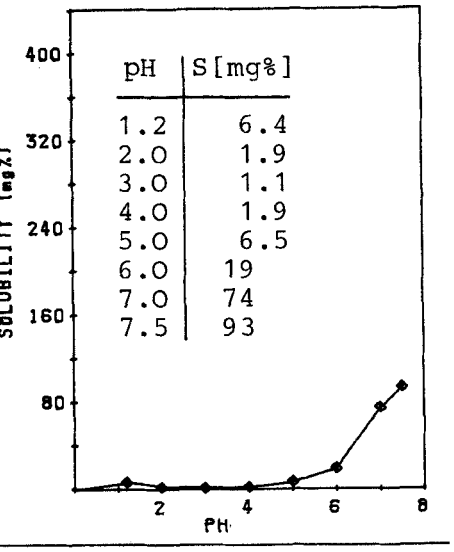
NIFLUMIC ACID MW 282.2

DISSOCIATION

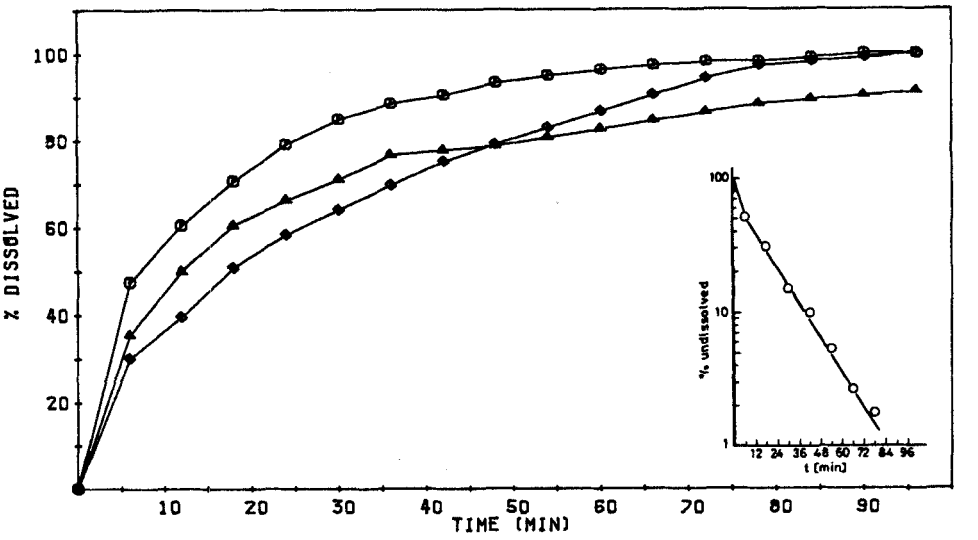


SOLUBILITY

pH	S [mg%]
1.2	6.4
2.0	1.9
3.0	1.1
4.0	1.9
5.0	6.5
6.0	19
7.0	74
7.5	93



DISSOLUTION RATE



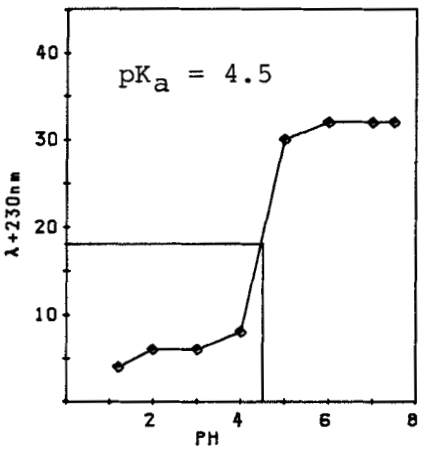
COMMENTS

The pK_a-determination is easily possible by the plot wavelenght vs. pH. The solubility of 6.4 mg% at pH 1.2 seems to be influenced by the solvent containing glycocoll (solubilizing ?). Two exponential phases of dissolution kinetics are indicated by the inside figure.

COMPOUND

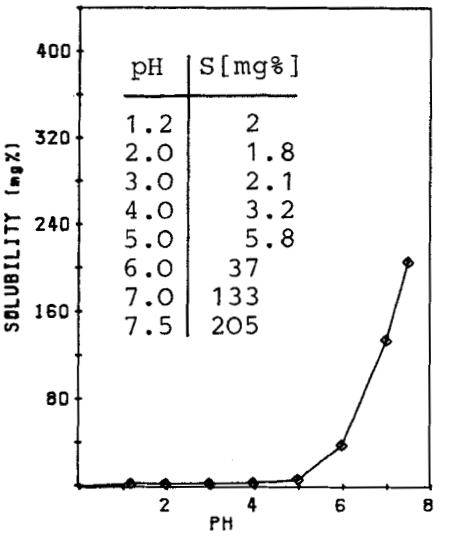
OXYPHENBUTAZONE MW 342.4

DISSOCIATION

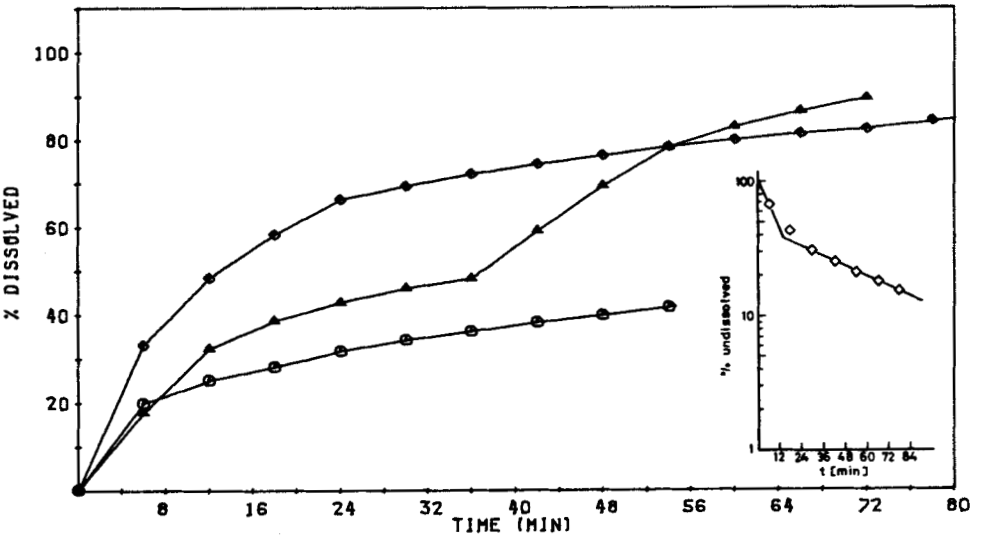


SOLUBILITY

pH	S[mg%]
1.2	2
2.0	1.8
3.0	2.1
4.0	3.2
5.0	5.8
6.0	37
7.0	133
7.5	205



DISSOLUTION RATE



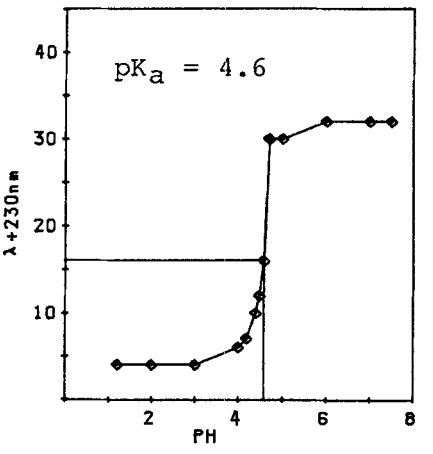
COMMENTS

pK$_a$-determination is easily possible by the plot wavelength vs. pH. Lit. data: pK$_a$ = 4.7 [14]. The solubility reaches about 200 mg% at pH 7.5 . The dissolution rates obviously differ. A two-phase exponential behaviour may be consideres (inside figure).

COMPOUND

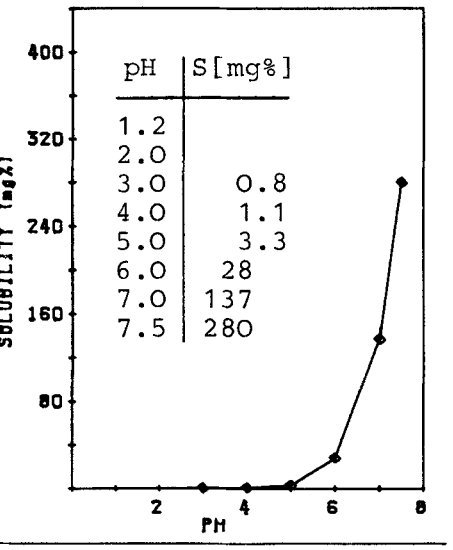
PHENYLBUTAZONE MW 308.4

DISSOCIATION

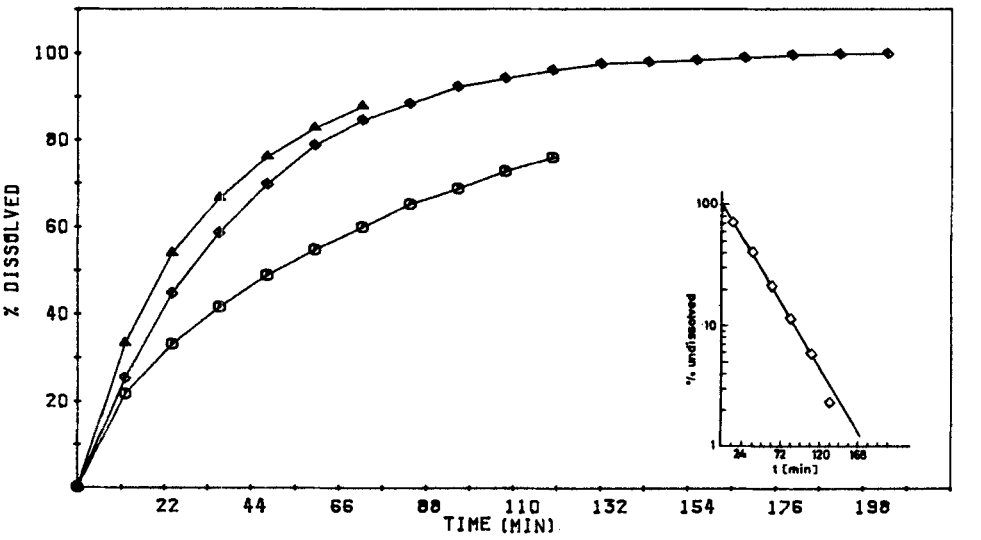


SOLUBILITY

pH	S[mg%]
1.2	
2.0	
3.0	0.8
4.0	1.1
5.0	3.3
6.0	28
7.0	137
7.5	280



DISSOLUTION RATE



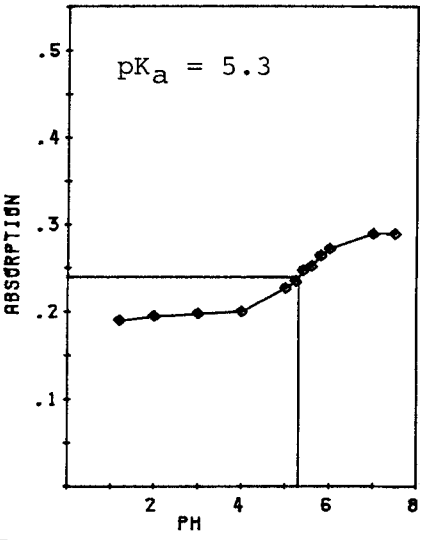
COMMENTS

pK_a-determination is easily possible by the plot wavelength vs. pH. Lit. data: pK_a = 4.5 [13]. The solubility at pH 2 is not measurable by the method proved. Dissolution rate determinations need approx. 1.5 hours to reach the 90%-level (one-phase exponential function).

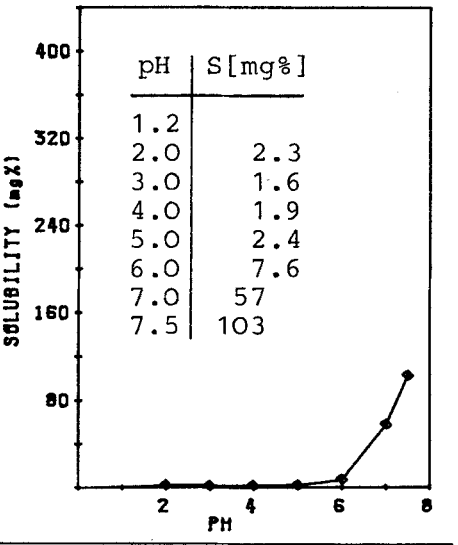
COMPOUND

PIROXICAM MW 331.3

DISSOCIATION

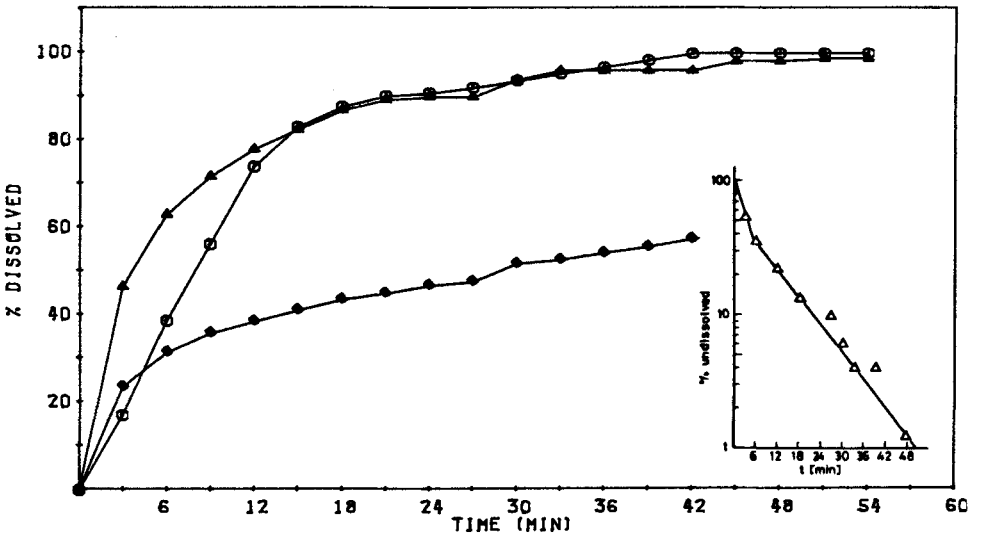


SOLUBILITY



pH	S[mg%]
1.2	
2.0	2.3
3.0	1.6
4.0	1.9
5.0	2.4
6.0	7.6
7.0	57
7.5	103

DISSOLUTION RATE



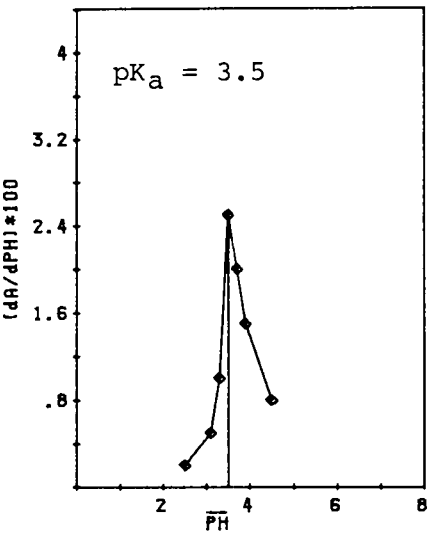
COMMENTS

pK_a-determination is easily practicable by the plot as shown. The solubility is very low up to pH 7.5 . Dissolution rates are different one to another. In one case of three a two-phase exponential behaviour is shown in the inside figure.

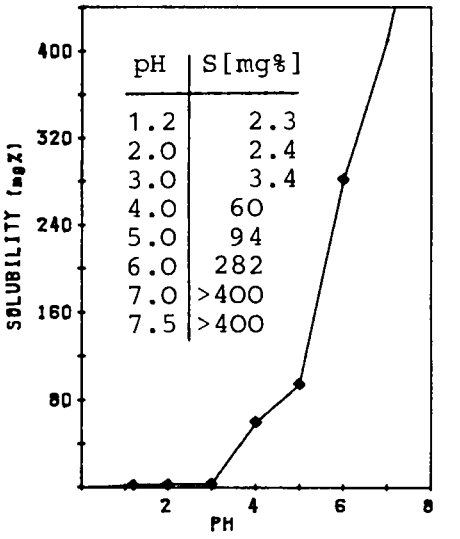
COMPOUND

TOLMETIN SODIUM MW 315.3

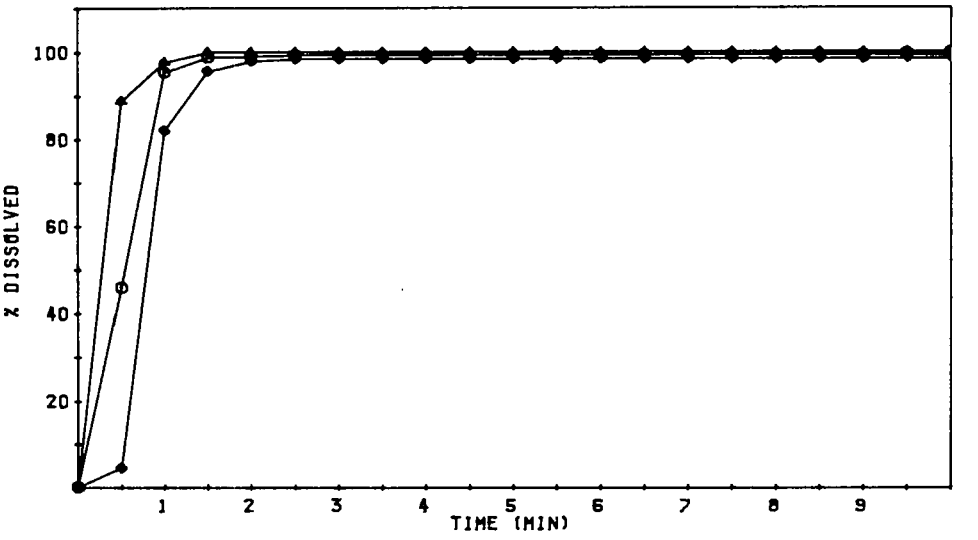
DISSOCIATION



SOLUBILITY



DISSOLUTION RATE



COMMENTS

pK_a-determination is easily possible by the plot shown. The solubilities at pH 7 and 7.5 are higher than 400 mg%. Very rapid dissolution rate.

ACKNOWLEDGEMENT

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