The intrinsic solubility of indomethacin

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Purpose

Indomethacin has been described as “practically insoluble in water” [1]; solubilities between 2-7 µg/mL have been reported [2,3]. However a higher value of 410 µg/mL has also been proposed [4]. Uncertainty undermines computational efforts to predict solubility [5]. Which value is correct?

Methods

The solubility of indomethacin was measured by two automated pH-metric titration methods. Firstly, a suspension of indomethacin in DI water was prepared at low pH and titrated with KOH solution. The data were compared with a Bjerrum curve calculated using intrinsic solubility, pK_a, sample concentration and pH. This curve depicts the disappearance of solid as it dissolves with increasing pH. Secondly, indomethacin was dissolved in ionized form at high pH and titrated with HCl until precipitation was detected. Thereafter, aliquots of KOH or HCl were added to maintain the system close to equilibrium, and the solubility was calculated from rates of pH change vs. concentration using mass and charge balance relationships.

Results

Solubility measured pH-metrically in experiments starting at low pH with original solid present was in the region of 4.0 µg/mL. Several attempts to measure solubility pH-metrically starting at pH 12 with re-precipitated sample present gave results of 400-500 µg/mL. It was then found that indomethacin decomposes at pH 12. Subsequent experiments starting at pH 9 gave results of 80 µg/mL. During some of these experiments, a sudden drop in solubility to around 10 µg/mL took place after several minutes at 80 µg/mL. It is suggested that these three measured solubilities (80, 10, 4 µg/mL) may represent the amorphous form and two crystalline forms.

Conclusion

Indomethacin can exist in forms with solubility between 80 and 10 µg/mL. However, the solubility of the most stable form appears to be in the region of 1 - 4 µg/mL.

References

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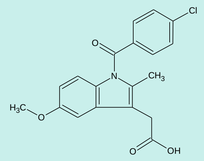
Solubility experiments # 6 – 9 in Table 1 were done using SiriusT3.

Some facts about indomethacin



Indomethacin is a non-steroidal anti-inflammatory drug. It is a carboxylic acid; the pK_a in 0.06 M ionic strength at 25°C is 4.13 [6]. It decomposes rapidly at high pH [7] to form p-chlorobenzoic acid and 5-methoxy-2-methyl-3-indoleacetic acid. It is reported to form aggregates in high ionic strength solutions and to form a poorly-soluble sodium salt [8]. It is known to form polymorphs; two of them, the α and γ forms, have been structurally solved. It can also form solvates, and its amorphous properties have been extensively studied [9]. Experimental aqueous solubility vs. time profiles for amorphous and crystalline indomethacin have been published [10], showing that the amorphous form was more soluble.

Measurements of indomethacin solubility

We measured the intrinsic solubility* of indomethacin by shake-flask at pH 1.42, and by potentiometric methods. Experiments # 6 - 9 were run under conditions chosen to avoid pitfalls listed above. They were run in low ionic strength conditions (to avoid salt formation). Titrations starting at high pH were not exposed to conditions above pH 9 (to avoid decomposition), and they were run in the presence of 50 µL of DMSO with 5 minutes of sonication at pH 9 (to aid dissolution).

Experiment #	Assay	Assay design	SOLUBILITY Kinetic µg/mL	SOLUBILITY Intrinsic µg/mL	Number of assays	Form switch observed?
		RESULTS FROM LITERATURE				
1	Yalkowsky [11]	Shake-flask?		0.94		
2	Avdeef [12]	pSOL. Determined using a cosolvent and extrapolation to 0% (w/w) cosolvent.		2.0		
3	Bergström [2]	pSOL. Determined using a cosolvent and extrapolation to 0% (w/w) cosolvent.		2.26		
4	Nokhodchi [3]	Shake-flask, at pH 1.2. 48 hour shaking, filtration, conc. by UV		3.88		
		RESULTS MEASURED IN THIS WORK				
5	Shake flask	200 mg in 20mL of 0.05M HCl, pH 1.42. 24 hr. shaking, 24 hr. sedimentation, conc. by UV.		4.01	1	
6	Curve fitting	pH2 ↗ up. 3.8mg in 1.5 mL DI water. Original solid present at start, dissolved during experiment.		3.31	1	
7	CheqSol	pH9 ↘ down. 2 ± 0.3mg in 1.5mL DI water + 50µL DMSO, adj. to pH9, 5 min sonication to dissolve sample	77.3 ± 10.1	9.4 ± 1.6	3	Yes
8	Curve fitting	pH9 ↘ down. 2 ± 0.3mg in 1.5mL DI water + 50µL DMSO, adj. to pH9, 5 min sonication to dissolve sample	68.7 ± 5.4	79.8 ± 5.8	3	
9	Curve fitting	pH9 ↘ down. 2 ± 0.3mg in 1.5mL DI water + 50µL DMSO, adj. to pH9, 5 min sonication to dissolve sample	72.1	13.2	1	Yes
10	CheqSol	pH12 ↘ down. 12.7mg in 10mL 0.15 M KCl.		417	1	

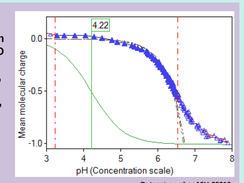
Results in purple represent the intrinsic solubility of the most stable crystalline form of indomethacin
Results in pale green probably represent the solubility of a more soluble crystalline form
Results in bright green probably represent the solubility of the amorphous form
Results in orange represent the solubility of a mixture of indomethacin and decomposition products

Table 1. Measurements of indomethacin solubility

*** Intrinsic solubility is the equilibrium solubility of the unionized form of the molecule. For indomethacin, an acid with pK_a of 4.2, this is equivalent to the solubility at low pH, e.g. below 2.2.**

Experiment 6 started at pH 1.8. 3.8 mg of indomethacin in 1.5 mL DI water + 50 µL DMSO was titrated with 0.5 M KOH. Dissolving solid was present, and some of the sample floated on top of the solution, leading to noisy data.

The large shift to the right of the Precipitation Bjerrum graph indicates that the solubility is very low (3.3 µg/mL).



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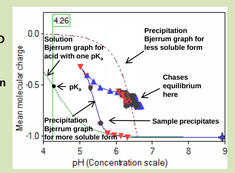
Experiment 7 started at pH 9. 2.2 mg of indomethacin in 1.5 mL DI water + 50 µL DMSO was titrated with 0.5 M HCl until it precipitated at pH 5.7.

Sample initially precipitated in a more soluble form (77.3 µg/mL) and then converted to a less soluble form (9.4 µg/mL), which persisted until the end of the experiment.



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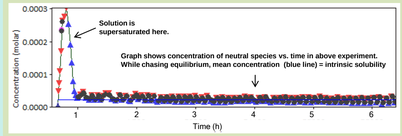
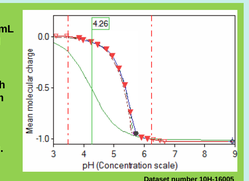
Experiments # 6–10 were carried out using Sirius’ patented [13] CheqSol method for measuring aqueous solubility. This method and its Curve-fitting version have been extensively described [14-17]. The graphs for experiment 7 (top right) are labelled to explain some of the features of the CheqSol method.



Experiment 8 started at pH 9. 2.2 mg of indomethacin in 1.5 mL DI water + 50 µL DMSO titrated with 0.5 M HCl; precipitated at pH 5.8.

The result was 79.8 µg/mL, with no evidence for change in form during the 34 minutes from precipitation to the end of the experiment. This result may represent the amorphous form.

This behaviour repeated in several experiments, but one behaved differently – see expt. 9.



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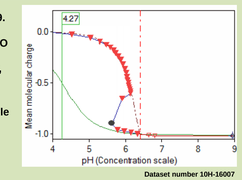
Experiment 9 started at pH 9. 2.0 mg of indomethacin in 1.5 mL DI water + 50 µL DMSO was titrated with 0.5 M HCl until it precipitated at pH 5.7, showing kinetic solubility of 72.1 µg/mL.

After precipitation, the sample quickly converted to a less soluble form (13.2 µg/mL).



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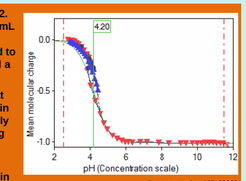
Solubility of 410 µg/mL?

Llinàs *et al* [4] published carefully measured values for the intrinsic solubility of 100 drugs, and invited readers to use them to train software to predict solubility of 32 measured but unpublished values. One of the unpublished values was indomethacin, 410 µg/mL. Difficulty was reported to predict this value [5]. It turns out that 410 µg/mL is incorrect, as explained here.

Experiment 10 started at pH 12. 3.8 mg of indomethacin in 10 mL 0.15 M KCl was titrated with 0.5 M KOH. The data appeared to chase equilibrium and yielded a result of 417 µg/mL.

Experiments later showed that the UV spectra of indomethacin solutions changed significantly after exposure to pH 12, owing to decomposition [7].

The result of 417 µg/mL represents mixed indomethacin and decomposition products.



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