# Imiquimod solubility in different solvents: an interpretative approach

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## BACKGROUND

Imiquimod (IMQ) is a synthetic drug FDA-approved for topical treatment and successfully formulated to date only as semi-solid lipophilic formulations. IMQ is poorly soluble in most solvents. Moreover, literature solubilities are discordant.

## AIM

This work investigates IMQ solubility in solvents suitable to develop innovative formulations, such as $H_2O$, ethanol (EtOH), methanol (MeOH), acetonitrile (ACN), and dimethyl sulfoxide (DMSO) to clarify literature discrepancies and collect reliable data.

## METHODS

IMQ solubility was assessed via HPLC from saturated solutions created by adding an excess amount of IMQ in $H_2O$, EtOH, MeOH, ACN, and DMSO kept at 30 °C under magnetic stirring until the solid–liquid equilibrium was reached (13 days). Supernatant solutions were then cooled at 25, 20, 16, and 4 °C to induce IMQ precipitation until equilibrium was reached again (2 days), then analyzed via HPLC. IMQ solutions in $H_2O$, EtOH, MeOH, ACN, and HCl 0.1 M were prepared, and their UV-Vis absorption spectra were recorded at 25, 40, 60, and 85 °C. NMR spectra of IMQ in deuterated chloroform, ACN, MeOH, and DMSO were recorded at 25 and 60 °C.

## RESULTS

### Exp. solubilities

| | 30 °C | 25 °C | 20 °C | 16 °C | 4 °C |
|---|---|---|---|---|---|
| $H_2O$ | 7.52 ± 0.08 | 6.10 ± 2.12 | - | 2.86 ± 0.62 | 0.58 ± 0.47* |
| EtOH | 541.06 ± 0.42 | 355.30 ± 41.21 | 288.96 ± 14.39 | 270.96 ± 13.70 | 191.18 ± 4.21 |
| MeOH | 491.16 ± 6.41 | 473.27 ± 7.09 | 373.25 ± 12.03 | 356.49 ± 53.90 | 348.80 ± 20.61 |
| ACN | 101.32 ± 4.75 | 100.14 ± 8.44 | 101.71 ± 10.76 | 101.40 ± 11.97 | 82.93 ± 1.20 |
| DMSO | 1382.27 ± 50.52 | 1116.78 ± 76.07 | 669.23 ± 6.16 | - | - |

**Table 1.** Experimental equilibrium solubility values of IMQ in $H_2O$, EtOH, MeOH, ACN, and DMSO at 30, 25, 20, 16, and 4 ° C expressed in μg $mL^{-1}$. Mean value ± standard deviation (n = 3).

### Exp. solubilities, total and partial Hansen solubility parameters

| | $\delta_{tot}$ | $\delta_D$ | $\delta_P$ | $\delta_H$ | $X_e$ |
|---|---|---|---|---|---|
| $H_2O$ | 23.4 | 7.6 | 7.8 | 20.7 | $4.59\ 10^{-7}$ |
| EtOH | 13 | 7.7 | 4.3 | 9.5 | $8.72\ 10^{-5}$ |
| MeOH | 14.5 | 7.4 | 6 | 10.9 | $8.07\ 10^{-5}$ |
| ACN | 12 | 7.5 | 8.8 | 3 | $2.22\ 10^{-5}$ |
| DMSO | 13 | 9 | 8 | 5 | $3.31\ 10^{-4}$ |

**Table 2.** $\delta_{tot}$, $\delta_D$, $\delta_P$, and $\delta_H$ [$(cal\ cm^{-3})^{1/2}$] for different solvents along with IMQ experimental solubility at 25 °C expressed as mole fraction ($X_e$).

### Ideal, regular and exp. solubilities

| °C | $X_2^i$ | $X_2$ | | | | | $X_e$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_2O$ | EtOH | MeOH | ACN | DMSO | $H_2O$ | EtOH | MeOH | ACN | DMSO |
| 30 | $4.62\ 10^{-4}$ | $7.03\ 10^{-66}$ | $1.60\ 10^{-23}$ | $4.29\ 10^{-28}$ | $5.97\ 10^{-13}$ | $1.60\ 10^{-23}$ | $5.66\ 10^{-7}$ | $1.33\ 10^{-4}$ | $8.37\ 10^{-5}$ | $2.24\ 10^{-5}$ | $4.10\ 10^{-4}$ |
| 25 | $3.78\ 10^{-4}$ | $4.63\ 10^{-67}$ | $5.41\ 10^{-24}$ | $1.22\ 10^{-28}$ | $3.04\ 10^{-13}$ | $5.41\ 10^{-24}$ | $4.59\ 10^{-7}$ | $8.72\ 10^{-5}$ | $8.07\ 10^{-5}$ | $2.22\ 10^{-5}$ | $3.31\ 10^{-4}$ |
| 20 | $3.08\ 10^{-4}$ | $2.78\ 10^{-68}$ | $1.76\ 10^{-24}$ | $3.30\ 10^{-29}$ | $1.51\ 10^{-13}$ | $1.76\ 10^{-24}$ | - | $7.10\ 10^{-5}$ | $6.36\ 10^{-5}$ | $2.25\ 10^{-5}$ | $1.98\ 10^{-4}$ |
| 16 | $2.60\ 10^{-4}$ | $2.73\ 10^{-69}$ | $6.99\ 10^{-25}$ | $1.13\ 10^{-29}$ | $8.48\ 10^{-14}$ | $6.99\ 10^{-25}$ | $2.15\ 10^{-7}$ | $6.65\ 10^{-5}$ | $6.08\ 10^{-5}$ | $2.25\ 10^{-5}$ | - |
| 4 | $1.55\ 10^{-4}$ | $1.74\ 10^{-72}$ | $3.72\ 10^{-26}$ | $3.72\ 10^{-31}$ | $1.36\ 10^{-14}$ | $3.72\ 10^{-26}$ | $4.37\ 10^{-8}$ | $4.69\ 10^{-5}$ | $5.95\ 10^{-5}$ | $1.84\ 10^{-5}$ | - |

**Table 3.** $X_2^i$, $X_2$, and mean $X_e$ of IMQ in $H_2O$, EtOH, MeOH, ACN, and DMSO at different temperatures.

### UV-Vis absorption spectra of IMQ solutions in HCl 0.1 M

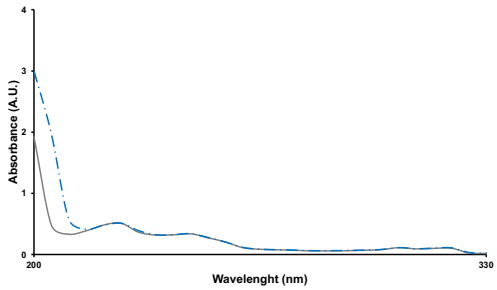


**Figure 1**. UV-Vis absorption spectra of a solution of IMQ in HCl 0.1 M at 25 (grey solid line) and 85 (blue dashdotted line) ° C.

### UV-Vis absorption spectra of IMQ solutions in $H_2O$, EtOH and MeOH

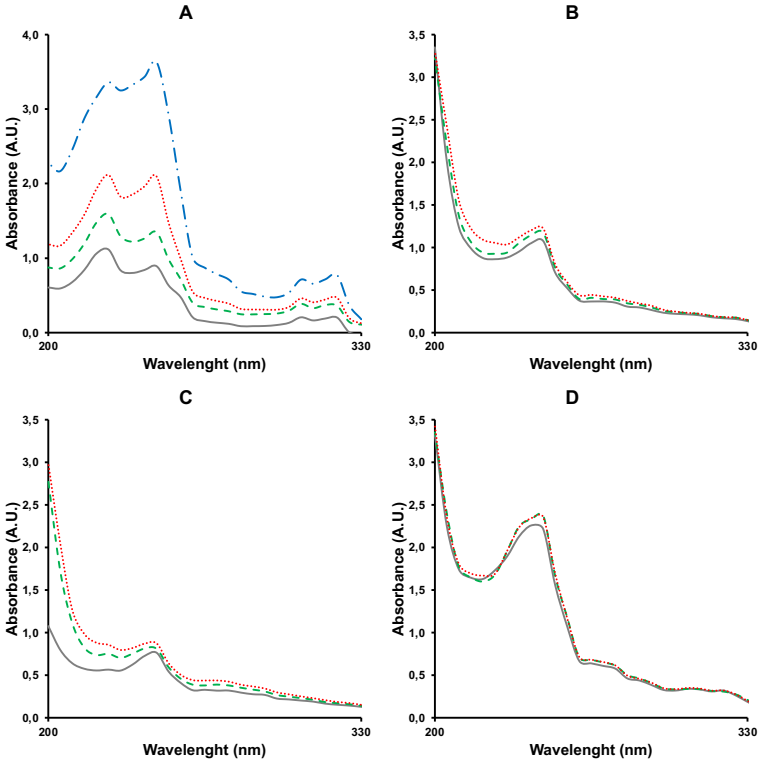


**Figure 2.** UV-Vis absorption spectra of solutions of IMQ in $H_2O$ (**A**), EtOH (**B**), ACN (**C**), and MeOH (**D**) at 25 (grey solid line), 40 (green dashed line), 60 (red dotted line), and 85 (blue dashdotted line) °C.

### $^1$H NMR spectra of IMQ

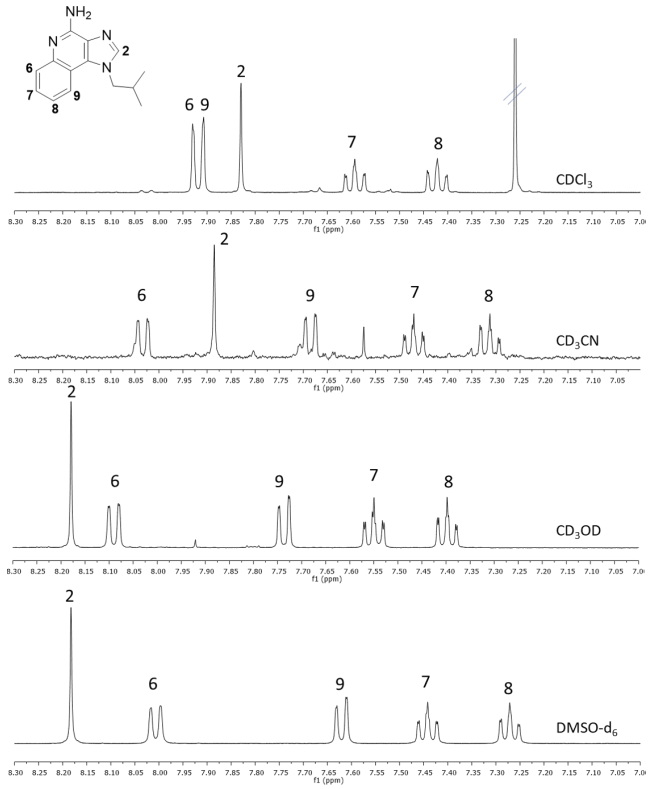


**Figure 3.** $^1$H NMR spectra of IMQ, 400 MHz at 25 ° C (spectrum region 7.00-8.30 ppm)

## CONCLUSIONS

IMQ solubility in $H_2O$, EtOH, MeOH, ACN, and DMSO was accurately determined at different temperatures. Experimental conditions, like temperature and stirring time, were found to significantly affect the time required to achieve complete dissolution. The Scatchard-Hildebrand equation does not apply to IMQ solutions studied because of association phenomena due to intermolecular hydrogen bonds involving the lone pair of the nitrogen atoms and the -$NH_2$ group indicated by the hyperchromic effect observed in UV-Vis absorption spectra, and/or π-stacking due to intermolecular overlapping of *p*-orbitals in the π-aromatic system indicated by NMR spectra.