

Determination of Aqueous Compound Solubility by a Modified Shake Flask Method

Purpose

Approximately 30% of drug candidate molecules fail early in development due to unfavorable physicochemical profiles. Poor solubility accounts for many of these PK failures [1]. Solubility is a thermodynamic parameter and is closely related to dissolution, a kinetic parameter. For ionizable molecules, pH plays a crucial role. A standard technique to determine the thermodynamic aqueous compound solubility is the shake flask method [2]. To make this method less time consuming the compound in this method is added to the buffer not as solid substance, but already dissolved in DMSO.

Assay protocol

Solubility measurement is performed under equilibrium conditions at pH 7.4. A highly concentrated solution of the drug in DMSO (usually 10 mM) is added to a standard buffer solution (pH = 7.4) up to saturation level indicated by undissolved excess drug. This saturated solution is shaken for 24h until equilibrium is reached. After separation from the solid phase by centrifugation, the concentration of the compound in the supernatant is determined by UV spectroscopy or LC- MS/MS.

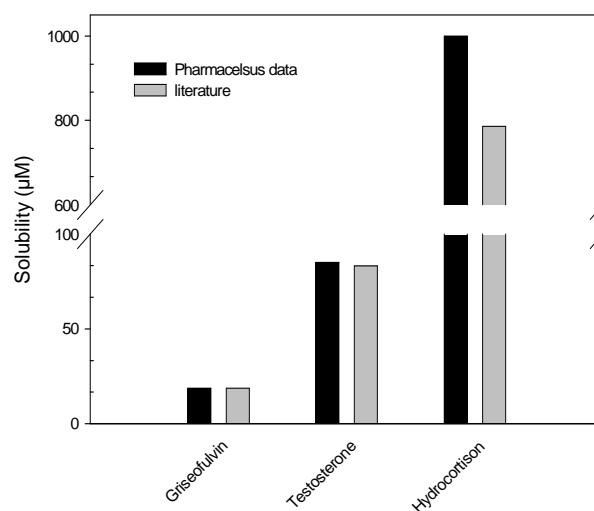
Model validation

Aqueous compound solubility of three drugs, tamoxifen, ketoconazol and hydrocortisone, with low, medium and high solubility, respectively, were chosen for assay validation. The data presented in figure 1 indicate that the solubility values obtained by this method correlate well with the published values [3, 4].

Literature

- [1] Avdeef A. (2001) Pharmacokinetic Optimization in Drug Research, B. Testa, H. Van der Waterbeem, G. Flokers & Guy R. (Eds). Wiley-VCH (Lausanne), 305.
- [2] ASTM: E 1148-02, Standard test methods for measurement of aqueous solubility, Book of Standards Volume 11.05
- [3] Kabasakalian et al, J. Pharm. Sci. 55:642 (1966)
- [4] Mosharraf and Nyström, Int. J. Pharm. 122:57 - 67 (1995)

Figure 1



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