

Cloe Screen Thermodynamic Solubility

cyprotexexperts in **ADME**

Background Information



'Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other property assays, mask additional undesirable properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the developability of the compound.'¹

¹Alsens J and Kansy M. (2007)
Advanced Drug Delivery Reviews
59; 546-567

- Poor solubility can limit the absorption of compounds from the gastrointestinal tract which reduces oral bioavailability. The quality of the data generated from the *in vitro* assays can also be affected by poor solubility.
- Compounds with poor solubility can pose a development challenge and result in prolonged development time frames and increased cost.
- Thermodynamic (or equilibrium) solubility investigates the solubility of a compound as a saturated solution in equilibrium.
- HPLC with UV detection is used as the analytical end point to improve selectivity of the response.
- The measured solubility is dependent on the pH of the solution at equilibrium and the pK_a of the compound.

Protocol

Compound Requirements

2.5 mg solid (for solubility assessment)
1 mg solid (for standard preparation)

Number of Replicates

n = 2 (aliquots from filtrate)

Incubation Time

Overnight

Incubation Temperature

Ambient temperature

Stirring

Vial roller system

Analysis method

HPLC- UV (photodiode array detector
acquiring between 220 nm and
300 nm wavelengths)

Data Delivery

Solubility (mg/mL)

In early development thermodynamic assays are performed to confirm earlier kinetic solubility results, to rule out potential artifacts, and to generate quality solubility data with crystalline material¹.

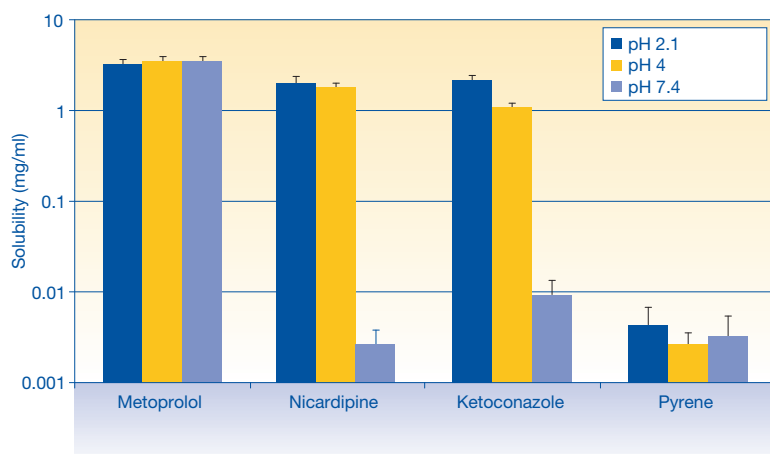


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4 compounds were screened through the Cloe Screen Thermodynamic Solubility assay at 3 different pH values. The results clearly demonstrate the ability of the assay to identify compounds which undergo pH-dependent solubility. As expected, both nicardipine and ketoconazole are more soluble at acidic pH whereas metoprolol and pyrene do not exhibit pH dependency over the range of pH values investigated.

Figure 1

Mean solubility data for 4 compounds generated in the Cloe Screen Thermodynamic Solubility assay at 3 different pH values (error bars represent the standard deviation of 3 separate experiments).



References

¹ Alsenz J and Kansy M. (2007) *Advanced Drug Delivery Reviews* 59; 546-567.