

API-Sparing Small Volume Dissolution and Solubility Profiling of Phenazopyridine.HCl

Background

Dissolution measurements of solid dosage form pharmaceutical products are traditionally carried out in standardized thermostatted baths accommodating USP volumes of 500 and 900 mL to maintain sink conditions during measurement.

However, when intrinsic dissolution experiments are performed in early development, volumes used are most often in the range of 175 to 250 mL, using a single beaker and Wood's rotating-disk apparatus, consuming up to 700 mg of pure compound in such mechanistic studies.

Saving API with the μ DISS™ Small Volume Dissolution Profiler

In response to the increasing interest in characterizing intrinsic dissolution in early development, where the API (active pharmaceutical ingredient) is not available in large quantities, a 6-vessel small volume dissolution instrument has been developed (Fig. 1).



FIG. 1 μ DISS Small Volume Dissolution Profiler

The integrated diode array spectrophotometer, controlled by the μ DISS Command Software, is used for *in situ* tracking and recording of a detailed dissolution profile. In the new μ DISS Small Volume Dissolution Profiler, the working volume can be as low as 2 mL, and as high as 20 mL may be used. While testing powdered APIs, magnetic stirring is used to agitate the suspension at a chosen speed. Currently, the μ DISS apparatus can be used for four purposes:

- 1) rank-order compounds by intrinsic dissolution
- 2) detect polymorphic changes
- 3) follow stability-time profiles and
- 4) determine equilibrium solubility.

During the various stages of synthesis scale-up, compounds may undergo polymorphic transformation. Replicate dissolution curves of the same sample at various stages of development may be used to spot this. An important additional feature of the small volume instrument is that equilibrium solubility can be measured when enough API is used. This is impractical in conventional 900 mL vessels, since too much API would be required to achieve the saturated solution needed to reach equilibrium.

The integrated photodiode array spectrophotometer follows the concentration of API as a function of time (*without having to filter the solution*), as seen in Fig. 2. In a conventional apparatus, several volumes of sample media must be removed for direct UV or HPLC/UV analysis during the dissolution experiment. This process is labor intensive and time consuming, requires volume corrections throughout the study, demands large-volume baths, and consumes significant amounts of precious API.

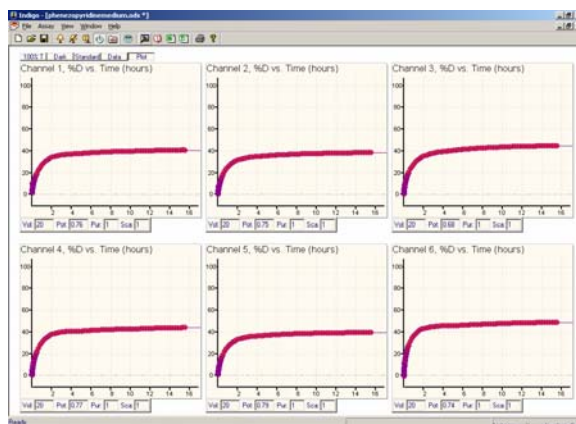


Fig. 2 μ DISS Command Software displaying 6-channel *in situ* dissolution and solubility of phenazopyridine.HCl in the small volume apparatus.

Data analysis becomes faster and more efficient when the UV data collection is performed directly in the dissolution vessel.

With the μ DISS apparatus, all moving parts have been eliminated from the data collection process. Thus, sampling errors due to sipper mechanism failure, sample contamination, filter clogging, adsorption to sampling tubing, etc., are not possible and cleaning up after analysis is a cinch.

Each channel of the μ DISS apparatus has a dedicated PDA (photodiode array) detector for fast, whole-spectrum UV data collection. With a collection speed of up to one full scan per second, a wide variety of dissolution rates can be measured in great detail.

Experimental

Phenazopyridine.HCl (Sigma), 0.75 mg, was weighed into each of six vials. (The surface area and particle size distribution of the compound were determined beforehand to be 1.31 m²/g; 64% of the particles were 10-40 μ m in size.) A fiber optic UV probe was lowered into each vial, and 20 mL of dissolution medium (0.05 M HEPES buffer, pH 7.4) were pipetted directly into each vial. The solutions were magnetically stirred at 700 rpm to achieve a short run-time for the dissolution/solubility experiment.

Results

The μ DISS Command Software can display and export dissolution data either as %D or μ g/mL. Fig. 3 shows the dissolution profile measured *in situ* at 25° C using the concentration scale (μ g/mL). In the first three minutes, it was possible to characterize the dissolution rates (inset in Fig. 3). The dissolution reached equilibrium in about 8 hours, with the solutions fully saturated. The red line indicates the predicted dissolution profile, using the μ DISS Dissolution Simulator Software (available late 2005), based on the Wang-Flanagan spherical particle model.

In Fig. 3, the concentrations are calculated by the μ DISS Command Software, based on a patented "on the fly" concentration analysis which enhances spectral features to eliminate *baseline distortions due to particle scattering*.

After about 18 hours, the concentration in each of the six vessels levels off to a constant value of 15.1 \pm 0.6 μ g/mL, very close to the 14.5 μ g/mL equilibrium solubility determined by an independent method.

The average dissolution rate for the six channels (Fig. 3 inset) was determined to be 44.3 \pm 0.6 μ g/mL/h (= 0.74 μ g/mL/min).

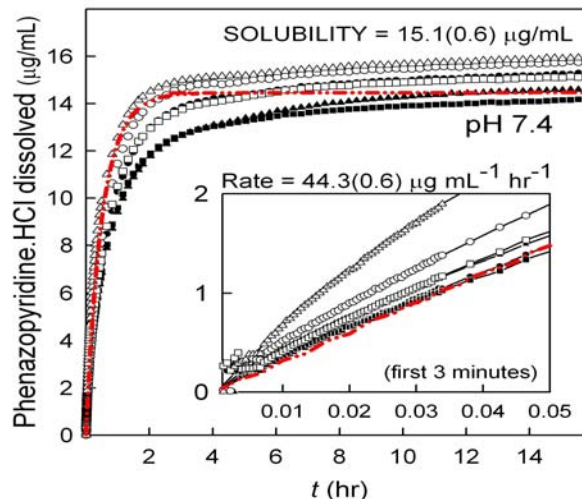


Fig. 3 SigmaPlot™ (SSI) software displaying the dissolution curve of Phenazopyridine.HCl in HEPES buffer at pH 7.4, using the concentration scale (μ g/mL). The inset is an expanded view of the first three minutes of data collection.

These results indicate that the μ DISS Small Volume Dissolution Profiler can be used to measure not only dissolution rate with good precision, but also equilibrium solubility at the chosen pH, using very small quantities of sparingly soluble APIs.

μ DISS Small Volume Dissolution Profiler

consists of:

μ DISS Small Volume Temperature Controllable, Stirring Sample Station

Integrated Type 2A photodiode array spectrophotometer, 6 independent channels, 6 UV probes (2-20 mm selectable path lengths).

μ DISS Command Software

Also required are:

External Circulating Water Bath

Pentium III PC Computer (minimum) with available PCI adapter slot, 512k of RAM, CD/RW disk drive, Windows XP operating system and color printer

