A novel experiment for assessing precipitation rates for ionizable drugs in supersaturated aqueous solutions

Jon Mole[1], Karl Box[2], John Comer[2], Martin Stuart[2]

[1] Sirius Analytical Inc, Lakewood, NJ, USA [2] Sirius Analytical Ltd, Forest Row, East Sussex, UK

Abstract

Purpose: To develop a method for assessing the rate at which ionizable molecules precipitate from supersaturated solutions after pH changes.

Methods: While many procedures exist for measuring dissolution rates, precipitation rates are difficult to measure. Data generated by CheqSol, a potentiometric procedure for measuring equilibrium solubility of ionizable molecules was used to calculate rates of precipitation and dissolution when the process is close to equilibrium in the presence of excess solid. Results are plotted as precipitation rate vs. concentration in solution, where precipitation rate is calculated from the rate of pH change per unit time as a function of the buffer capacity and the average molecular charge. Positive rates indicate that the substance is precipitating; negative rates indicate that it is dissolving.

Results: From data for 70 ionizable drugs, molecules were identified in three classes. Molecules in the first class precipitate and dissolve slowly (e.g. ibuprofen precipitates and dissolves at rates between 5 – 10 µM/min). Molecules in the second class precipitate quickly but dissolve slowly (e.g. nortryptyline precipitates almost instantaneously but dissolves at 5 – 10 µM/min). Molecules in the third class precipitate slowly but dissolve quickly (e.g. tolmetin precipitates at 2 – 6 µM/min, but dissolves almost instantaneously). The crystalline state of two molecules was found to change irreversibly during the experiment, and it was observed that rates of precipitation and dissolution were significantly different for their different states. Some molecules repeatedly precipitated in one form but re-dissolved in another form with lower solubility, presumably after undergoing a change in crystal habit after precipitation (e.g. phenobarbital precipitates at 50 µM/min with solubility of 5.5mM but dissolves at 10 – 30 µM/min with solubility of 4.7mM – see graph).

Conclusion: A method for measuring precipitation rates of ionizable drugs from supersaturated solutions has been developed. Several different classes of precipitation and dissolution have been identified.

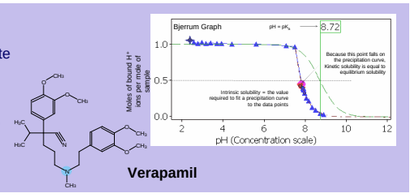
pH-metric solubility measurement

CheqSol measures the solubility of ionizable drugs that form supersaturated solutions by the method described on the center page.

Not all drugs form supersaturated solutions. As the pH of a solution of base in ionized form is raised and increasing amounts of neutral form are created, some drugs precipitate immediately without supersaturation. We call these molecules non-chasers, because they do not chase equilibrium. Although they precipitate very quickly, non-chasers can be quite slow to dissolve.

The unionized form of many non-chasers is a liquid at room temperature (photo shows pramoxine after centrifugation at high pH). Nearly all the non-chasers we have found are bases, and they are normally formulated as salts, which have a higher MP and are easier to crystallize. Non-chasers have little or no hydrogen bond donor capacity. The Bjerrum graph for non-chasers is quite different to that for chasers.

Verapamil is a **non-chaser**. The neutral species of verapamil can't form a supersaturated solution. It precipitates as soon as the solution reaches an appropriate pH. The precipitation point, as well as all pH points after precipitation fall on the precipitation Bjerrum curve. The kinetic solubility of non-chasers is equal to their intrinsic solubility. Solubility is determined by fitting the data to the theoretical Bjerrum Curve. The solubility of verapamil is 48.7µg/mL.



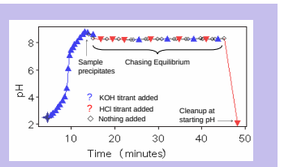
Verapamil

An overview of CheqSol

THE EXPERIMENT

Metoclopramide is a **chaser**. A weighed sample is dissolved at pH 2.5 (as BH^+), and then titrated with 0.5M KOH until it precipitates at pH 8.85 from a **supersaturated solution**. The pH then quickly drops to about 8.3 as unionized sample (B) falls out of solution, and is replaced in solution as BH^+ converts to B and releases H^+.

After the pH stabilizes, **Chasing Equilibrium** begins. Small volumes of HCl ? or KOH ? titrants are added, and the rate of pH change is monitored. Adding HCl converts B to BH+ and consumes H+ ions; the sample dissolves, and the pH goes up slightly. Adding KOH converts BH+ to B and releases H+ ions; the sample precipitates, and the pH goes down slightly.

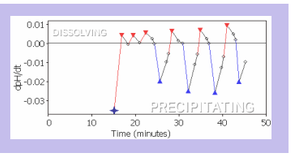


Metoclopramide

GRAPH OF $\frac{dpH}{dt}$ VERSUS TIME

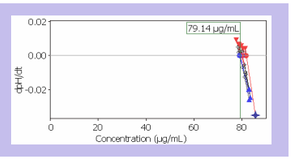
Just before the pH of each point is recorded, the rate of change of pH is also recorded. Here, the rate of change $\frac{dpH}{dt}$ is plotted vs. time. For bases, rates are positive when samples are dissolving, and negative when they are precipitating*. At the crossing points when rates are zero, the sample would be at equilibrium solubility.

** opposite for acids*



THE EQUILIBRIUM CHASING CROSSOVER PLOT

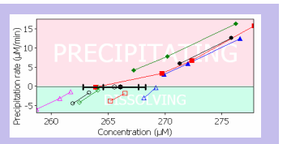
Using mass balance and charge balance equations, the concentration of B in solution is calculated at each point. When consecutive points are plotted vs. concentration and connected with straight lines, they intersect on the Y = 0 axis at a concentration equal to the **equilibrium solubility result**. The solubility of metoclopramide is 79.14µg/mL.



THE PRECIPITATION RATE GRAPH

When the precipitation rate of unionized species B (i.e. change of concentration C vs. time) is defined in terms of pH change, buffer index (BI) and average molecular charge, and plotted vs. concentration, it shows the rates of precipitation and dissolution when the sample is close to equilibrium.

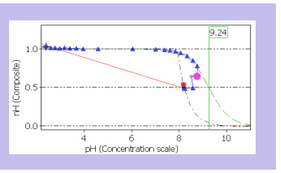
$$\text{Precipitation rate} = \frac{dC}{dt} = \frac{-\frac{dpH}{dt} \times BI}{\text{Average molecular charge}}$$



THE BJERRUM CURVE

The titration curve can be re-plotted as a Bjerrum curve to reveal **useful diagnostic information**.

The points on the green dotted line show the data up to the point of precipitation. The Y = 0.5 intercept denotes the aqueous pK_a. The mauve disc denotes the precipitation point. All points while chasing equilibrium fall on the Precipitation Bjerrum Curve (brown dashed line).

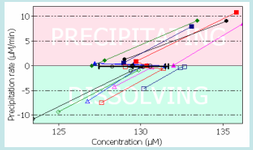


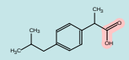
FOUR CLASSES OF EQUILIBRIUM SOLUBILITY OF IONIZABLE MOLECULES

Chasers

Molecules that precipitate slowly from supersaturated solutions, and also dissolve slowly from crystalline solids.

Well over half the marketed drugs we have measured have been chasers, which can be acids, bases or ampholytes. Chasers are well-behaved; The graph below shows an chaser, Ibuprofen. Many drugs in development are not chasers.



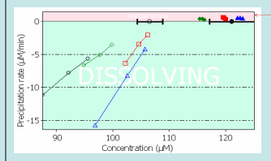


Ibuprofen

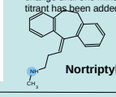
Non-chasers

Molecules that precipitate quickly without supersaturating, but dissolve slowly.

About 20% of the bases we have measured have been non-chasers. We rarely see acid non-chasers. Most non-chasing drugs show good BBB uptake. They tend to have little or no capacity to donate hydrogen bonds. The graph below shows a base, Nortryptiline.



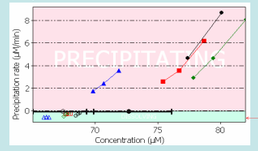
No data here, because Nortryptiline precipitates so fast and we don't collect data using our standard procedure, which doesn't start monitoring rate of pH change until one minute after titrant has been added

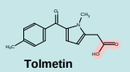


Nortriptyline

Super-chasers (or Super-dissolvers)

Molecules that precipitate slowly and dissolve quickly. We have seen only a few examples of super-chasers. The graph below shows an acid Tolmetin. Other examples include Papaverine (a base) and Chlorzoxazone (an acid).





Tolmetin

No data here, because Tolmetin dissolves so fast and we don't collect data using our standard procedure.

Ghosts

Molecules that precipitate quickly and dissolve quickly.

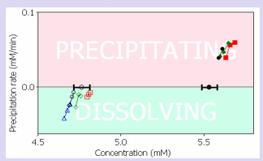
We postulate the existence of this class of molecule, but we have never seen a drug that shows this behaviour.

We would be able to measure its solubility by the same method we use to measure non-chasers. Data collection would be very fast, and all the data points would fall on the precipitation Bjerrum Curve, both for titration with KOH and with HCl.

PRECIPITATION RATE SIGNALS CHANGES IN CRYSTALLINE FORM

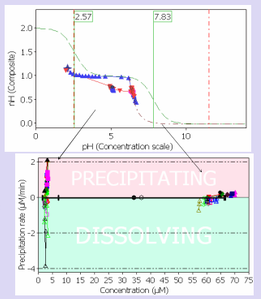
Precipitating as one crystalline form, yet dissolving as another

This graph shows Phenobarbital. The data suggests that after it precipitates, phenobarbital converts into a different form which is harder to dissolve and has a lower solubility. Many drugs show similar behaviour, including sulfamerazine, ketoprofen, benzthiazide, thyroxine and ciprofloxacin.



Precipitation and dissolution rates of different polymorphs

These graphs show Boehringer Ingelheim sample BIX011397, which converted from one polymorph to another during a Cheqsol experiment. The dissolution and precipitation rates of the two polymorphs are different, and one is much more soluble than the other.



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Tel: +44 1342 820720, Fax: +44 1342 820725
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