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# Measuring solubility automatically with vision

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**Solubility measurements are critical to the development of any chemical process. Recently in *iScience*, Shiri et al. describe a modular, "human-out-of-the-loop" platform that uses visual data rather than typical analytical techniques such as high-performance liquid chromatography to determine when a compound has dissolved.**

> "If only you could see what I've seen with your eyes."—Roy Batty in *Blade Runner*

Measuring the solubility of a compound in various solvents is a fundamental first step in the development of a chemical process across multiple industries, whether it be commodities, fine chemicals, pharmaceuticals, or materials. Both determining how to dissolve a compound in order to perform some chemical reaction or purification and understanding the solvent conditions that allow for downstream processing and isolation start with this measurement.[1] In addition, as continuous processes increase in importance in pharmaceutical manufacturing, finding a common solvent system that is suitable for a range of steps and operations is of great importance.[2]

Various methods have been developed for measuring solubility; some of them can be conducted in a semi-autonomous, high-throughput manner, but all rely upon fairly similar steps.[3] Although a variety of standard analytical techniques are then deployed to make the actual measurement (the amount of solute in a given amount of solution), the most common is high-performance liquid chromatography (HPLC). Although solubility predictions have made progress and can provide trends and rough estimates,[4] the experimentally determined value is still desired. Altogether, this complex workflow entails a high cost in terms of either labor (if manual) or equipment (if conducted on an automated platform with HPLC). In fact, an industrial consortium has even issued a challenge to build a system to take on these issues.[5]

Recently in *iScience*, Shiri et al.[6] describe a pragmatic, modular solution for making this measurement by using "off-the-shelf" components and open-source software to enable a fully automated workflow. A number of innovative features are described in this platform, but of particular note is the clever use of visual data to gauge turbidity and thereby determine at which point enough solvent has been added to fully dissolve the solute. A simple webcam and custom algorithm made this advance possible.

The entire workflow itself brings together a number of common, automated unit operations, namely (1) a robotic arm for vial manipulations, (2) a liquid handler, (3) solid dosing on a balance, (4) a stir plate, and (5) a webcam. To bring these subunits together, Shiri et al. mounted them on a deck and orchestrated their operations with a Python script. Importantly, they showed that individual components, in this case the robotic arm, are easily exchangeable and agnostic of manufacturer. Moreover, the entire platform is able to measure solubility in the absence of human interventions. The net effect is to have a truly open-sourced solubility measurement alternative to more sophisticated commercial systems.

In actual practice, the system mimics much of how a human would make this measurement by using an "excess solvent" type of method that relies upon determining the end point of solvent addition through visual observation of complete dissolution of a weighed amount of solute. Figure 1 provides a step-by-step summary of the individual unit operations: (1) a solid is weighed out on a Mettler-Toledo Quantos weigh station, (2) a liquid handler (in this case a Tecan Cavro syringe pump with N9 controller) delivers an initial charge of solvent while the sample vial sits on a stir plate, (3–6) the webcam, and associated algorithm, captures images on a small region of interest and continues to add solvent in a stepwise manner until it appears that all solids have fully dissolved, (7) the vial then gets transferred back to the balance for a final weight (with both mass and volume of solvent added), and a report with all measured values and calculated solubility is generated, and finally (8) the "next experiment" is then determined.

To transport the vial between the various stations, the authors showed that either an N9 (SCARA) 6-axis robot arm or a Kinova Gen3 7-axis arm could be used interchangeably with the Python script and controllers. The data reporting was accomplished by real-time experimental updates through Slack. Also, as depicted in Figure 1, there is a logic gate at step 6 to determine whether the solids are dissolved or

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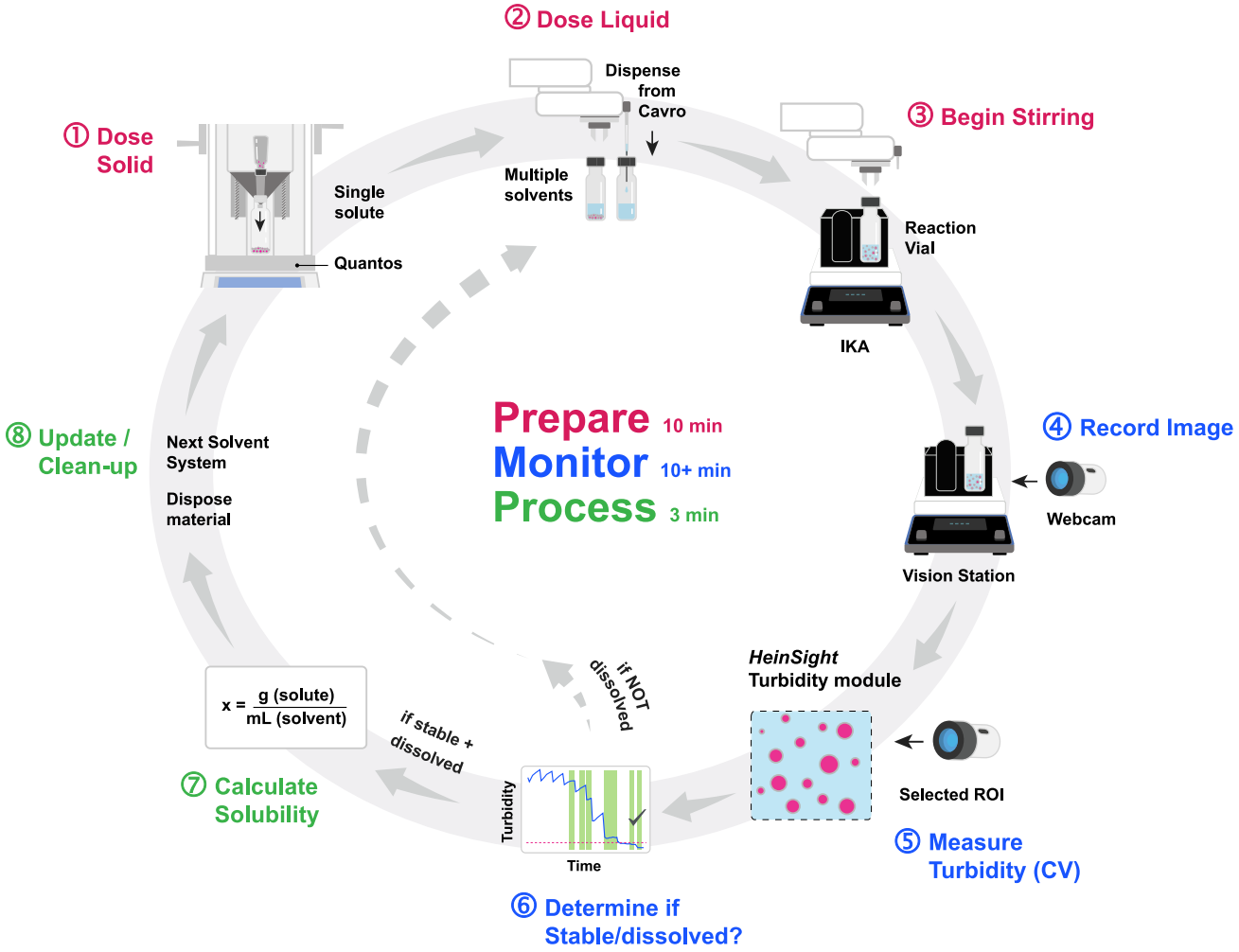


**Figure 1. Automated workflow overview**

(1) A fresh HPLC vial is uncapped and transferred to the Quantos, where a pre-specified amount of solid is dispensed. The vial is then recapped and transferred to the vision station. (2) A pre-specified initial volume of solvent is dispensed into the vial with the solid and stir bar. The system starts stirring in (3). In (4), (5), and (6), turbidity monitoring takes place. In (7), the solubility is calculated based on solid mass and final solvent volume. In (8), the used vial is returned to the tray and the system updates initial values in preparation for the next experiment. Figure and legend reprinted from Figure 3 of Shiri et al.[6]

whether the workflow needs to return to step 2 in order to add more solvent.

Importantly, Shiri et al. benchmarked the performance of their system by using caffeine's solubility in five different solvents versus an established "excess solid" manual slurry filtration method. Although they observed variations in terms of accuracy and precision, the obtained values with their automated platform were certainly sufficient to guide process development. They then went on to show that equivalent solubility values could be obtained with either robotic arm on caffeine or tetrabenazine (TBZ) in various solvents. Certainly, additional refinement of the system and its experimental environment could improve upon these initial results.

The authors do note some current limitations of their described system: the color and contrast of the solute relative to its background, the lack of a controlled environment in terms of temperature and lighting, and the ability to run multiple experiments in parallel. Improvements in the visual recognition system along with a controlled lighting and background stage could certainly address some of the aforementioned limitations. Environmental controls, automated, interchangeable solid dosing dispenser heads, and multiplexing of vials could later address some of these other challenges in terms of throughput. In addition, with continued advances in semi-empirical and extrapolated solubility predictions, the ability to measure solubility across multiple solvents, mixtures, and temperatures will become less pressing and thus make a few, select automated measurements more valuable.

This is an impressive advance in automated solubility measurements built from simple, readily available components and code. The confluence of ever-more sophisticated machine-learning techniques, readily available automation components, data handling, and the ability to stitch together these pieces to replicate common laboratory procedures conducted by humans is a harbinger for a future where the design, execution, and analysis of experiments are enabled by intelligent, automated laboratories.[7] Further, the barrier to building and operating such systems is clearly limited only by the creativity of the researcher and not by the cost or complexity of the process.

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