CASE STUDY

Enabling Hydrogenation for Route Development in a Pharmaceutical Process Development Lab

The process development group at a pharmaceutical company has a broad number of roles and responsibilities. However, a primary role is the application of chemis try and chemical engineering to the scale-up of new synthetic processes from the laboratory, on to the pilot plant, and then to full-scale manufacturing in a plant. The techniques employed cover a wide range of chemistries and technologies including both batch and, more commonly, continuous processes.

Process development remains a challenging area for a number of reasons. Chemists and chemical engineers routinely come across chemistries, which are difficult or hazardous to scale-up, while maintaining yields optimized on a laboratory scale (if optimized at all!). Furthermore, the technologies available on a laboratory scale are not often available or realizable on a larger scale (e.g. microwave reactor technology).

Process development groups are continually searching for enabling technologies that will either allow difficult chemistries to be scaled or improve the safety of certain processes. This use case will cover both.

THE NEED

In this particular example, a process development group at a Pharma company is currently in need of high pressure hydrogen generation. There is a continual shift both internally and externally for the removal of hydrogen gas cylinders or lecture bottles on the basis of safety. Furthermore, current methods of operation require the changing every 25-30 minutes for some applications. This creates an additional safety risk and incurs a high cost.

The H-Genie hydrogen generator (Genie) is a newly developed hydrogen generator specifically for chemists and chemical engineers, which can be used to produce 4.0 hydrogen gas up to 1NL/min and 100 bar. To date, it is the only hydrogen generator designed specifically for chemists that can generate pressure and work with both batch and flow reactors. The below is a report on how well the H-Genie™ operated in a process development lab.

REPORTING

Setup

The system was installed in ~15 minutes and was a simple procedure. It requires outlets for venting hydrogen, water and oxygen. Manual has clear setup instructions.

Start-up

The Genie was found to be very simple to get up and running. The system does an internal pressure test to 110bar on startup and has completed this stage in ~5 minutes. This is quicker than the current low pressure hydrogen gene rators which can take up to 20 minutes to generate low pressures. Once comp lete it is then possible to set the reaction conditions.

Navigation

The menus are well laid out, easy to navigate and the screens have the right amount of information. The touchscreen is responsive and there hasn't been a case of trying to press one button and it activates another. The flow and batch modes are very easy to operate by selecting reaction pressure and vessel fill rate for batch mode or gas flow rate for flow mode as shown in Figure 1.

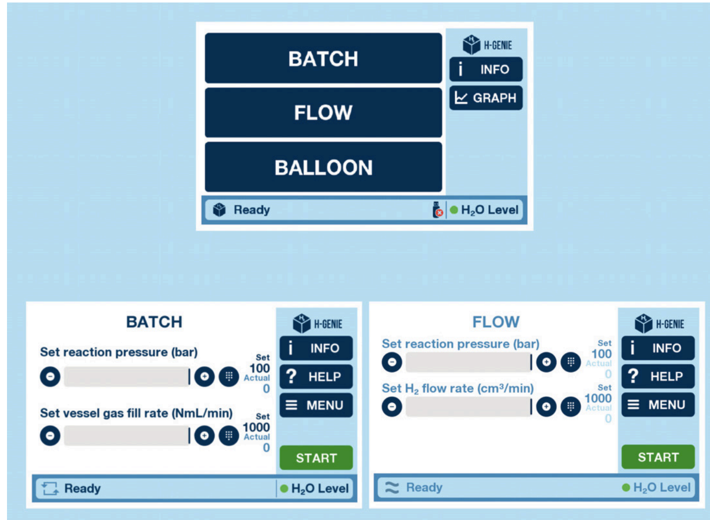

figure 1

Flow-rate Accuracy

When conducting experiments with continuous proces ses, it is important to have accurate flow rates. The flow rates are controlled through an internal mass flow controller (MFC), which also logs the amount of hydrogen released from the system (important in the case of logging hydrogen uptake during a reaction). The H-Genie™ was tested over a series of flow-rates multiple times and an average taken. Results are displayed in the table below.

Flowrate	Average (nml/min)	% Difference from Setpoint	Max (nml/min)	Min (nml/min)
100	99.59	-0.41	108.39	96.16
500	509.16	+1.83	516.01	496.61
1000	1010.48	+1.05	1045.79	999.03

LAB RESULTS

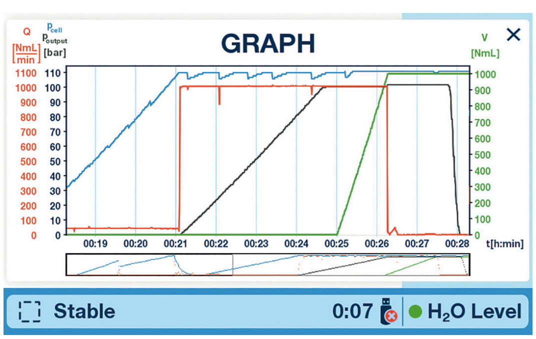

figure 2

From an industrial perspective, the high pressure capability of the H-Genie is very important to allow the following:

- Increase dissolution of the hydrogen gas in solution to increase both the likelihood that the reaction will proceed and to speed up the reaction further.
- To allow heating of the reaction mixture to speed up the reactions without volatility and vaporizing of the solvent.

Several debenzylation reactions were reacted at pressures ranging from 20-80 bar at a temperature of 80°C both with a hydrogen cylinder and with the H-Genie. There was no difference in results between hydrogen cylinder and the H-Genie.

The user really liked the ability to monitor reaction in real time in the form of of a graph and export the data as a .csv file. (Figure 2.)

The H-Genie performed well in most tests. The H-Genie fits a gap in current capability by allowing larger scale hydrogenations to be run without the use of lecture bottles while also providing a safer alternative. The users found the device simple to setup and operate.

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