

Liquid dispensing

Simplifying dose-response and drug-synergy testing experiments with the Multidrop Pico 8 digital dispenser

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Keywords

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Abstract

Dose-response testing is widely used in pharmacology, toxicology and drug discovery research. However, experimental setup is often error-prone due to the manual, multi-step process. In this application note, we show that it is possible to automate dose-response assay setup and enhance reliability and throughput with the Thermo Scientific™ Multidrop™ Pico 8 Digital Dispenser. Additionally, the Multidrop Pico 8 digital dispenser simplifies drug-drug interaction studies by assisting the design of multidrug synergy experiments. These workflows—enabled by the Multidrop Pico 8 digital dispenser—are broadly applicable to many research disciplines, supporting new laboratory efficiency and experimental precision.

Introduction

The Multidrop Pico 8 digital dispenser is a reagent dispensing system that streamlines dose-response experiments through the automation of tedious manual procedures. Featuring high levels of precision and reliability, the system makes it possible to set up assay plates with greater speed and accuracy. It directly delivers picoliter-sized fluid drops into standard microwell plates or custom well plates. Its ability to meter drops created at the rate of up to 160,000 drops per second supports serial, dilution-free workflows because of a wide dynamic range of dispensing—from picoliters to microliters. Removing serial dilution steps conserves precious compounds or reagents, allowing users to reduce experimental time and costs (Figures 1 and 2) while reducing ergonomic risks associated with highly repetitive procedures.

The instrument does not require calibration thanks to the precision of the microfluidic dispense head and the digital nature of counting drops, helping assure high reproducibility for virtually any experiment that requires liquid dispensing. Dispensed volumes are recorded in a report for users to review afterward and leverage for data analysis steps.

The Multidrop Pico 8 digital dispenser dispenses user-defined volumes into target wells. The total dispense volumes are calculated by Thermo Scientific™ Multidrop™ PicoIT Software, and users are prompted to pipet a given volume into a dispense head before the run. A cartridge contains either 8 or 4 dispense heads for increased sample throughput. The maximum volume to be pipetted into the dispense head is 20 µL for the 8-channel cartridge and 200 µL for the 4-channel cartridge. The dispense head and the loading cup are built with chemically resistant materials, enabling a user to dispense dimethyl sulfoxide (DMSO), a standard solvent for small molecules, alcohol, weak acids and aqueous buffers. In addition to small molecules, it is possible to dispense biomolecules (DNA, RNA, protein) and nanoparticles. The cost-effective, single-use cartridges are ideal for preventing cross-contamination between experiments while minimizing waste.

The Multidrop Pico 8 digital dispenser offers several user-friendly features that make it useful for a range of laboratory needs. Multidrop PicoIT software enables users to create, edit and operate a dispensing protocol with ease. The software offers a graphical user interface complemented by experimental setup wizards designed for a variety of applications, including dose-response, multidrug synergy, enzyme kinetics and polymerase chain reaction (PCR). The software's digital workflow simplifies reaction normalization and well randomization to help mitigate skewed results (Figure 2). Lastly, the Multidrop Pico 8 digital dispenser can be integrated into a fully automated workflow, including the instrument, consumables and software application programming interface (API).

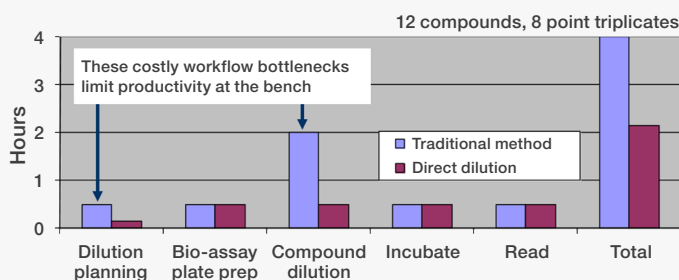


Figure 1. The Thermo Scientific Multidrop Pico 8 Digital Dispenser decreases the overall workflow time from 4 to 2 hours.

Data courtesy of Daniel Beacham, PhD, Thermo Fisher Scientific

This application note highlights the key features and advantages of setting up and running a dose-response experiment on the Multidrop Pico 8 digital dispenser, including data provided by multiple Thermo Fisher Scientific customers.

Materials and methods

Protocols were created using Multidrop PicoIT software. To investigate drug-drug interaction, 2 compounds were tested at 8 concentration levels, ranging from 30 nM to 10 µM in a single replicate. Both compounds were dosed in linearly spaced concentrations: Compound A at 0, 0.1, 1.75, 3.4, 5.05, 6.7, 8.35 and 10 µM and compound B at 0, 0.03, 1.69, 3.35, 5.02, 6.68, 8.34 and 10 µM. The software's synergy wizard was used to automatically set up the plate layout, which has 64 wells total, testing different combinations of both compounds as well as each compound on its own. DMSO levels in each well were normalized so that every well had the same DMSO concentration. Compounds were pipetted onto dispense heads on a cartridge as directed by the Multidrop PicoIT software. Once the dispensing was completed, the plate was processed in a downstream assay to measure the effect of drug combinations.

Table 1: The Multidrop Pico 8 digital dispenser can save up to 90% of library compounds for dose-response tests.

	Series	Serial dilution compound needed	Direct dilution compound needed	Relative compound requirement	Compound usage reduced
Customer 1	11 points x 3	30 µL	3 µL	10%	90%
Customer 2	8 points x 2	15.4 µL	2 µL	12.9%	87%
Customer 3	9 points x 2	20 µL	2 µL	10%	90%
Customer 4	11 points x 3	60 µL	7.5 µL	12.5%	88%
			Average	11%	89%

Data courtesy Jennifer Smith, PhD, Harvard Medical School

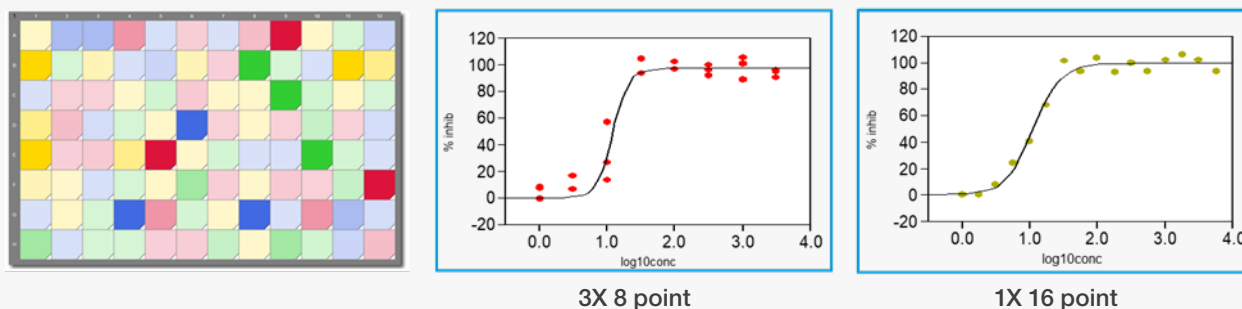


Figure 2. The Thermo Scientific Multidrop Pico 8 Digital Dispenser supports randomization along with various titration modes, resulting in high-precision data for dose-response tests.

Data courtesy of SIGA Technologies, Inc.

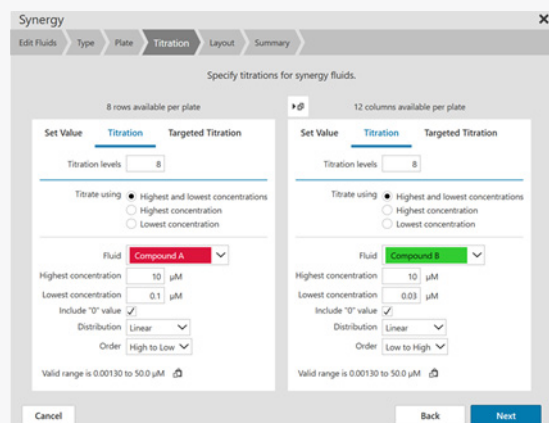
Table 2: Equipment and consumables used in the example workflow.

Equipment and consumables	Cat. No.
Thermo Scientific Multidrop Pico 8 Digital Dispenser	5840600
Thermo Scientific™ Cartridge for Multidrop™ Pico 8 Digital Dispenser, 200 µL, 4-channel	LTR0003
Thermo Scientific Cartridge for Multidrop Pico 8 Digital Dispenser, 20 µL, 8-channel	LTR0004

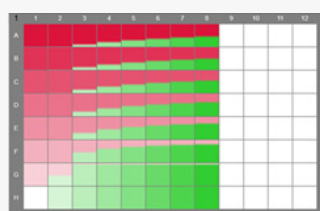
Results

Drug-drug interaction studies using the Multidrop Pico 8 digital dispenser are simple to set up. These experiments took only 5 minutes to create a dispensing protocol (Figure 3A) and complete the dispensing. Two compounds are depicted in shades of red (compound A) and green (compound B) in the plate layout in Figure 3B. No compound control (well H1) and single compound controls (wells A1 and H8) were included. Compounds A and B showed the high level of synergy (warm color) in the synergy surface plots in Figure 3D, with the highest level of synergy observed at 0.6~3 µM for compound A and 1.8 µM for compound B.

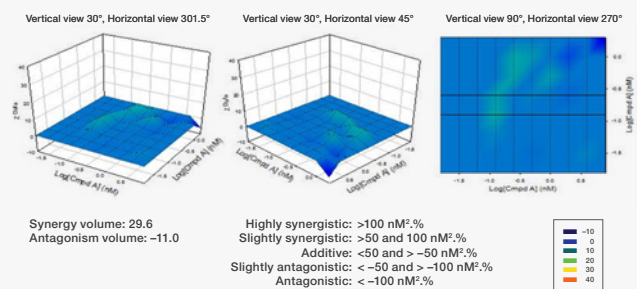
3A.



3B.



3C. Synergy surface of compound A vs. compound A



3D. Synergy surface of compound A vs. compound B

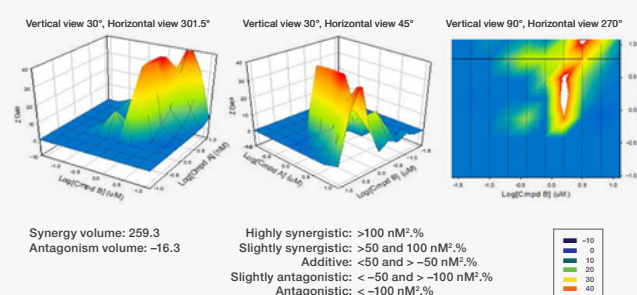


Figure 3. The Multidrop Pico 8 digital dispenser supports a multi-drug synergy study by providing a simple protocol design using Multidrop PicoIT 8 software. The synergy wizard sets up an experiment (3A) and creates the synergy plate layout automatically (3B). Compound A was titrated against itself as a control (3C). Synergistic interaction between compounds A and B is demonstrated (3D).

Data courtesy of Michel Perron, PhD, and Rob Jordan, PhD, Gilead Sciences, Inc.

Both compounds showed additive effects in some concentration ranges (blue or cool color), but no antagonism (Figure 3D). A control experiment, where compound A was co-titrated against itself, showed an additive effect, not synergistic, as expected (Figure 3C).

Conclusions

The Multidrop Pico 8 digital dispenser enabled efficient investigation of the multidrug combination space to identify the potential drug-drug interaction. Use of the digital dispenser for this experiment resulted in significant time savings by removing serial dilution steps and shifting to direct compound dilution. Furthermore, direct dilution with the Multidrop Pico 8 digital dispenser allowed for a single 10 mM stock of each compound to be used, reducing compound expenditure and increasing the number of concentrations tested. This workflow is widely applicable to a variety of research disciplines, including drug development, drug metabolism and pharmacokinetics (DMPK) studies, enzyme kinetics assays and more.

The following advantages of adopting the digital dispenser for the demonstrated workflow should be noted:

- High-precision performance
- Dispensing various solvents, including DMSO, aqueous buffers, alcohol and weak acids
- Accommodating standard and custom plates
- Large dynamic range
- Time and cost savings
- Supporting various titration modes (by volume, concentration and targeted titration)
- Normalization and randomization
- Automation-ready capabilities
- User-friendly software

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