Doing More with Less:

How the MatriStore Has Dramatically Improved Efficiency at Neurocrine Biosciences

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LIFE SCIENCE SYSTEMS

In 2004, Neurocrine Biosciences was one of the top biotech companies in San Diego. The company's stock price had reached over $70 per share, its market capitalization was over $4 billion, based on the future valuation of a drug designed to treat insomnia. Neurocrine attracted top talent from all over the world. The organization had over 500 employees, including more than 50 medicinal chemists. In 2004, Neurocrine moved into a brand new and state-of-the-art campus in Del Mar, California. To support its talent, the company invested heavily in the latest R&D technologies. The goal was to develop new drugs to help cure diseases for the general population.

One of the purchases made was a Matrical MatriStore (now Brooks Life Science Systems) storage system. The system was designed for fully automated microplate and tube storage and retrieval. Towering 30 feet tall, the MatriStore was so large that the new science building was designed around it. The MatriStore can hold 200 trays, each tray measuring 8 feet by 4 feet, providing total capacity for about 33 million samples. Storage conditions were optimal at -20° C with very low relative humidity. The samples had to be kept dry since DMSO takes on water easily. They also were kept in the dark for protection from ultraviolet light. The robotics allowed for up to 20,000 sample retrievals in 24 hours. Neurocrine purchased the system knowing the sample collection would grow over 10 years. The company added 100,000 new samples each year from purchased libraries as well as in-house synthesis.

The MatriStore purchase allowed much more efficient operation. Compound management is a highly labor-intensive process and the MatriStore helped ease that process. For instance, individual selection of "cherry picking" compounds was limited to no more than 1,000 samples per week with a high chance of introducing error. Samples went through many freeze/ thaw cycles, which led to compounds crashing out of solution, massive condensation in the freezers, and untracked volumes of samples in microplates. The goal of Neurocrine's high-throughput synthesis group in its medicinal chemistry department was to design and synthesize compound libraries as quickly as possible. This process included, but was not limited to, improving potency at the receptor, addressing solubility issues, increasing stability, and decreasing off-target liabilities. High-throughput chemistry is used to answer as many of these questions as possible concurrently rather than serially.

Designing libraries did not require much time, but producing them was too slow. Gathering large numbers of reagents was the most time-consuming process in setting up the libraries. On average it took 1 to 2 weeks to assemble the reagents. Some of the reagents needed to be ordered from suppliers, and these materials had standard 1-week shipping times if in stock. Chemical suppliers also use a wide range of container types, which meant they could only be stored manually. No robotic system can store random bottle types. Chemicals also came in multi-use containers, which meant the amount used could not be tracked. Once all of the reagents were gathered and inventoried, the department had to label, tare, and weigh them in standard 14 mL vials designed for automation. Only after this process was completed could the team synthesize a library of compounds.

Automating the Process

The high-throughput synthesis group questioned why it kept using such a slow, repetitive process of chemical handling when the biology group had simplified their process years earlier by moving to industry-standard SBS racks. The breakthrough came when the high-throughput synthesis team believed it could store reagents in microtubes in the MatriStore. By borrowing the idea to standardize chemical storage in SBS plates, the team dramatically improved its efficiency (see figure 1).

The automation project started with the storage of safer chemicals — such as amines, alkyl halides, carboxylic acids, aldehydes, and ketones — in solution. The group avoided putting the highly reactive chemicals, such as acid chlorides, into the MatriStore because of concerns about generating HCl.

The reason chemicals were put in solution, was to move them much more easily. The group experimented with a few dilution solvents. DMSO didn't work well because the reactions were messy when the chemicals were heated to high temperatures, plus it generated side reactions with unwanted impurities. The group also tried DMF, but it proved too reactive. This led the team to N-Methyl-2-pyrrolidone (NMP) due to it being inert, having a high boiling point and low freezing point, and no evaporation. These chemicals were put in 96-well Matrical minitubes with airtight heat seals.

Did It Work?

There were general concerns about storing chemicals using robotics. NMP is not a typical solvent used in reactions mainly because the boiling point makes it difficult to evaporate, and it also takes on water like DMSO. Another concern was long-term chemical storage in polypropylene plates instead of glass. After 7 years of storage, the lab is still using the chemicals and they are still reactive. The success rate today is the same as before. This makes sense because the chemicals are stored in the dark at -20° C at low humidity in air-tight, single-use tubes. The team has an accurate inventory of every chemical in the MatriStore. Compare this with the old procedure where the chemicals were stored at ambient temperature, the bottles were continuously opened and closed, and the amounts were not tracked after removal.

More importantly, in the most common reactions such as acylations and alkylations, diluting with NMP has not been a problem and provides the same yields as traditional solvents. NMP also has worked successfully in very difficult reactions such as the Suzuki coupling and reductive aminations. And finally, the MatriStore hasn't shown any signs of corrosion.

Overall, the project has been a large success and has streamlined synthesis at Neurocrine. The organization hasn't experienced any disadvantages to storing chemicals in NMP versus neat, unless the material is super-reactive. Inventory is now 100% accurate, and the specific volumes and concentrations in each tube and well are known. The analysis has shown the cost to produce compounds has dropped from $1,000 per compound to less than $10. In 2004, the group produced about 15,000 compounds while in 2013, it produced over 35,000. The proof of concept is in the numbers and automated chemical storage has proven its value.

Figure 1: Compounds contained in a wide range of container types were stored in SBS plates.

About the Author

Derrick Miyao earned his B.S. from the University of California-San Diego in 2003 and started as an intern at Neurocrine Biosciences in the pharmacology department. He is now a research scientist in the medicinal chemistry department where he uses technology to be more efficient.

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