Innovations in Cell Culture Technology Drive Drug Discovery Studies

Tanuja H. Mohite

Department of Computer Science and Engineering, SVERI's College of Engineering, Pandharpur

Third Year Engineering Student

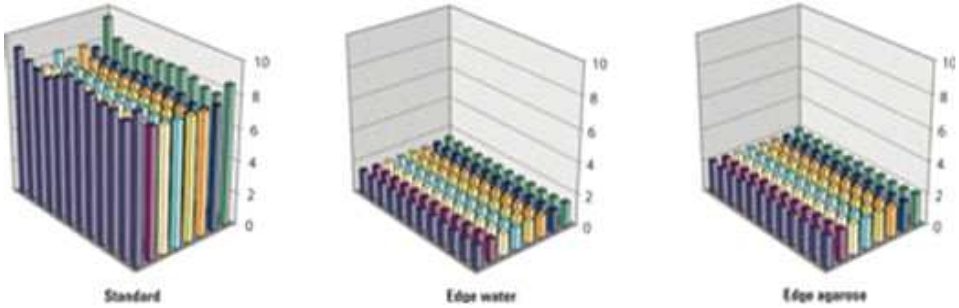

Figure 1. Moat design significantly reduces evaporation during seven-day incubation when compared to a standard plate. Image: Thermo Fisher Scientific

Scientists around the world make use of cell culture techniques on a daily basis. Whether they happen to be working with primary cell cultures, secondary cultures or cell lines, they all face many of the same problems: slow growth, spontaneous differentiation, evaporation, contamination and a host of other issues that require troubleshooting.

In the fields of drug discovery and screening, these problems can directly impact data accuracy and reproducibility. With drug discovery programs costing millions, even billions of dollars, issues that affect an assay's reliability can waste precious time and money—something most laboratories can't afford to lose. As we demonstrate here, recent advances in cell culture consumable technology have endeavored to solve many of these problems experienced by those at the bench.

Taking cell culture to the edge:

Making use of microplates is commonplace in cell culture laboratories as they offer a great deal of efficiency, providing high-quality and consistent culture conditions in a relatively small space. However, a common complaint around microplate cell cultures is the problem with evaporation, or the "edge effect." Due to the small volumes of media used within each well, those located around the perimeter of the microplate are subject to evaporation during long periods of incubation. This can lead to changes in media pH, osmolality and the concentration of the media constituents, with potentially problematic consequences for cell assay results. Screening for lead compounds typically rests upon having efficient, reliable and usually automated methods of cell culture,

meaning that evaporation across a plate is likely to result in unnecessary assay noise and a significant increase in plate rejection.

Without any clear solution to this problem, cell culture scientists frequently leave those wells on the perimeter empty. This equates to a 37.5% loss of available culture wells on a 96-well plate, and a significant loss in throughput. Technology such as the Thermo Scientific Nunc Edge 96-well plate overcomes the issue of the edge effect by making use of a "moat" around the perimeter of the plate. The moat, which is filled with sterile fluid, can significantly reduce evaporation both at the perimeter and across the entire plate (Figure 1). Ultimately, this means long periods of incubation are unlikely to affect either cell viability or the validity of an assay.

With such a reduction in evaporation across all wells, it becomes much easier to ensure that cell culture conditions are uniform across a microplate, which in turn improves assay consistency and maximizes the predictive accuracy of the information generated. Now, researchers can make use of their entire microplate with confidence during cell-based assays for anticancer drug screening and disease modeling.

Scratching the surface of Parkinson's:

It isn't just environmental factors like evaporation that can affect the success of cell culture; there's also the very surface of the plates themselves to consider. Cells can adhere to the plate's surface, which can affect the development of a culture. Stem cells in particular are notoriously challenging to work with, and are subject to problems like spontaneous differentiation in response to random adhesion to the plate surface. Stem cells are utilized in multiple avenues of research because of this very ability to differentiate, but this differentiation needs to occur in a controlled and predictable manner.

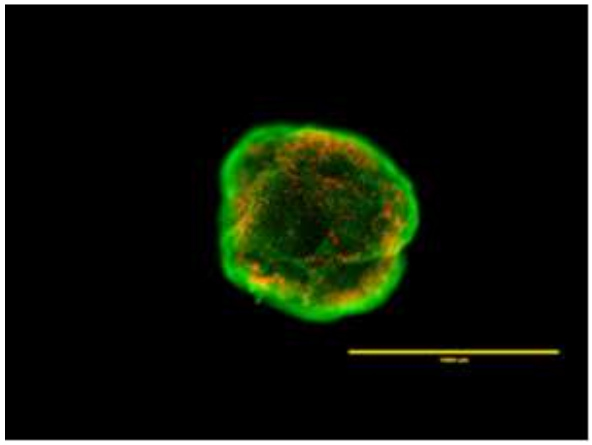

Figure 2. Human embryoid body (EB) generated on the Thermo Scientific Nunclon Sphera round-bottom 96-well plate in the Essential 6 Medium (formerly Life Technologies) containing TGF-β, cell viability evaluated by the LIVE/DEAD Cell Viability Assays (formerly Life Technologies). Image: Thermo Fisher Scientific

An important intermediate step in the differentiation process is the formation of spheroids, such as embryoid bodies (EBs) (Figure 2). The composition of the plate's surface coating can result in variability across a group of EBs, so it becomes important to optimize and control surface conditions for successful and viable cultures. Nowhere is this more relevant than in laboratories making use of EBs for medical research.

In a joint study by Thermo Fisher Scientific and the Parkinson's Institute and Clinical Center, Staff Scientist Chetana Revankar, PhD, and her team are using gene editing and stem cell differentiation techniques to investigate Parkinson's disease as a means to further our understanding of the disease and find effective new treatments. As such, Dr. Revankar uses EB cultures to generate neural stem cells for her research into Parkinson's. She cultures single EBs in individual wells, allowing better control of the size and viability of the EBs.

According to Dr. Revankar, this comprehensive project looks closely at Parkinson's disease by differentiating induced pluripotent stem cells to neural stem cells and neurons in vitro to be used in disease-modeling. In short, they are reproducing Parkinson's in a dish.

A key element of the study has been ensuring that each EB was as similar to other EBs on the microplate as possible. Interactions with the plate surface can cause variations within the culture, which can drastically skew data. To minimize such variations, the research team is using the Thermo Scientific Nunclon Sphera round-bottom 96-well plates. These plates utilize a specialized surface that prevents the absorption of extracellular matrix proteins that would otherwise lead to the cells adhering to the surface and promoting cell aggregation. This, together with the size and shape of the well bottom, allows the researchers to generate a single EB in each well with an excellent level of consistency.

Conclusion:

Researchers require that cell-based assays achieve high efficiency and high throughput; therefore, the cell culture consumables used need to meet exacting standards when it comes to performance, quality, precision and safety. This is particularly critical in drug discovery and screening where researchers need to demonstrate a high degree of reproducibility. Recent innovations to surface and plate technologies have provided greater consistency and improved cell viability within assays, allowing researchers to meet the demands of a competitive and challenging field of research.