Smoothing the transition: liquid, dry powdered media, and advanced granular technologies

Formulating a cell culture medium that supports your cells to produce a high-quality biologic in the greatest yield is an essential part of the R&D process. When progressing through clinical stages, choosing the optimal format for scale-up is critical. While sourcing smaller volumes of liquid media at the early stages of development can be convenient, considering storage and supply chains becomes key as media volumes increase. While each cell culture media format has its own advantages and disadvantages, it is important to assess the format that is most suitable for the current and future needs of your process by considering scalability, cost-effectiveness, and convenience.

Scaling up production

The use of liquid media is often economical and appropriate at the R&D scale. However, as you scale up, the cost of storing or outsourcing bulk process liquids must also be considered. Increasing volumes can result in higher shipping fees and increased storage requirements. Large areas of facilities may become dedicated to liquid media storage, reducing available space for production, and costs might increase with additional investments in third-party storage solutions. However, these extra costs may be outweighed by the convenience of prepared liquid media. The use of liquid media is significantly less labor-intensive and requires fewer quality checks, due to the larger batches made possible by outsourcing production. It is worth considering the appropriate volumes of liquid media to purchase, because the shelf lives of liquid media are shorter than those of powdered formats that can be stored prior to reconstitution. Due to this fact, the purchase of a liquid medium should be carefully planned to ensure the medium can be used before expiry. Another key advantage of the liquid media formulation is the inherent scalability, since components are more easily distributed throughout the medium.

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The popular choice

Dry powdered media (DPM) are currently the most popular choice for large-scale production—with around 90% of catalog, custom, and proprietary media purchased as powder and reconstituted in-house [1]. A key difference between liquid media and DPM is the reduced footprint required to store DPM, leaving more facility space to manufacture and store your valuable biologic. Further, having the flexibility to reconstitute DPM as required removes the need to store large volumes of liquid media to meet future demand. On-demand reconstitution is possible due to the longer shelf life of DPM. Finally, the shipping cost of DPM is significantly lower than for liquid media because dry media weigh less.

While liquid media are generally ready to use, DPM require additional preparation, including weighing, hydration, and mixing, as well as adjustment of pH and osmolality upon reconstitution. This makes DPM more labor-intensive and time-consuming than liquid media. They can also present safety issues to bioprocess operators: the handling of strong acids and bases and exposure to dust generated by the powders necessitate additional protective equipment and procedures. Another challenge presented to bioprocess operators is maintaining lot-to-lot consistency. This is a particularly troublesome challenge in large-scale GMP production, where consistency is essential. The introduction of improved milling technologies—such as FitzMill™ and pin mills—has improved the homogeneity of DPM. However, some biopharmaceutical manufacturers still share concerns about the preparation of DPM. This is not to say that DPM are not consistent, only that achieving consistency can be more complicated than it is with liquid equivalents, since experienced personnel and strict protocols are required. Choosing a trusted media supplier is very important to minimize these challenges.

Not all powders are created equal

Both liquid media and DPM present advantages and disadvantages that create an opportunity in the workflow for a format with the economic benefits of a powder and the expediency of a liquid. This opening is being filled by newer granulated dry formats. The Gibco™ Advanced Granulation Technology™ (AGT™) dry media format addresses limitations associated with conventional DPM, including poor solubility and variation between batches [2], as well as the need for adjustments after reconstitution. Figure 1 demonstrates the equivalency of AGT and liquid media. The titers, growth, and viability of Gibco™ ExpiCHO-S™ cell clones are comparable in both liquid and reconstituted AGT Gibco™ ExiCHO™ Stable Production Medium (SPM) formats.

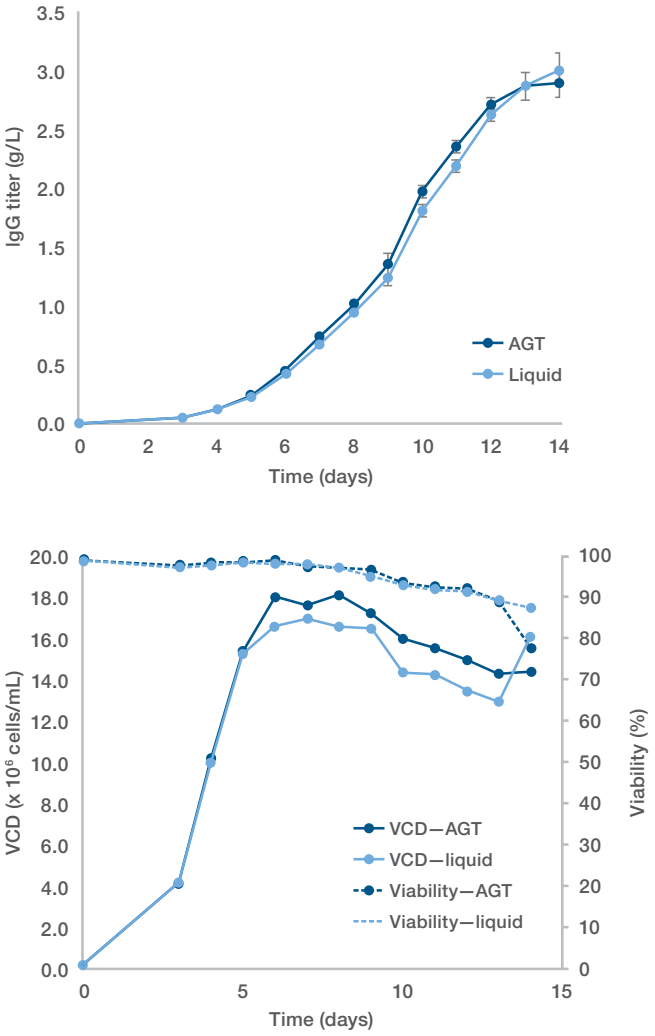

Figure 1. Consistent time courses of productivity and growth in liquid and AGT media formats. The titers, growth trajectories (VCD: viable cell density), and viability of ExpiCHO-S clones in liquid and reconstituted AGT ExpiCHO SPM were comparable. Each value is reported as the average of 12 replicates.

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The AGT format is considered a single-component powder as it is homogeneous in nature and does not require added ingredients, simplifying supply chains. The larger granules created in the AGT manufacturing process dissolve more rapidly during mixing and do not produce dust, so reconstitution does not require bioprocess operators to wear additional protective equipment.

The format is also found to be consistent across scales, making it a suitable format for applications from research to commercial manufacturing. This equivalency allows for the adoption of AGT media over a range of scales, even smaller scales where liquid media are typically preferred. AGT media can also be purchased in small non-GMP batches, making it simple to optimize formulations and seamlessly transfer to a GMP medium during scale-up. This allows rapid evaluation of media formulations and formats, which streamlines process development.

The simpler hydration process possible with AGT media increases productivity, saves time, and reduces bioprocessing and regulatory risks. With flexibility and speed-to-market being important priorities for the biopharmaceutical industry, AGT media effectively bridge the gap between conventional DPM and bulk liquids. However, the nature of a granulated medium means the formulation must be reconstituted in-house. While this offers flexibility that is not available with bulk liquids, it does require the capacity to reconstitute a sufficient volume of medium for the process. Evaluating your current capacity and requirements when choosing a granular or powdered medium is essential to avoid surprise costs as you scale up.

Rapid prototyping: Smoothing the transition

Choosing the optimal format for scale-up can present a number of challenges, and there are a number of things to consider to make the process as smooth as possible. The key challenge is understanding your formulation; performance could be affected by scaling up or switching from a liquid to a powder format. The formulation could require alterations to maintain its performance in an alternative format. Failure to evaluate these changes early could lead to unexpected redevelopment costs to optimize the medium.

Determining whether your process could benefit from an alternative format is important, particularly when making a large investment during scale-up. This stage can be risky when you are unfamiliar with a format, even when the benefits are clear. To help ease your transition to an alternative—such as AGT, traditional DPM, or liquid media—Thermo Fisher Scientific offers rapid prototyping services. As part of the service, non-cGMP rapid manufacturing is available for smaller batches of custom or proprietary media for process development and format evaluation prior to outsourcing full cGMP manufacturing of the finalized formulation. This includes options for formulation optimization and changes in raw materials. The quick turnaround times and flexibility of rapid prototyping, even with proprietary formulations, allow your projects to stay on track so you can focus on bringing your valuable biologics to the patients they benefit.

References

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