Peptide Synthesis for the 21st Century

GAPPeptides™

GAP Peptide Synthesis

Scalable, Efficient, Economical

Innovating peptide synthesis in the 21st century is demanding. It requires robust, flexible, cost-effective, and highly efficient process technologies coupled with advancements in sustainability that make peptide-based products more affordable and safer for consumers. To put it simply, useful innovation must be relevant and attainable - delivering tangible benefits from process to product. It requires the ability to scale up from a benchtop flask to a multi-kg scale while meeting market demands faster and cheaper. This must also be done while meeting or exceeding regulatory guidelines and delivering improvements to the environmental impact of the manufacturing process.

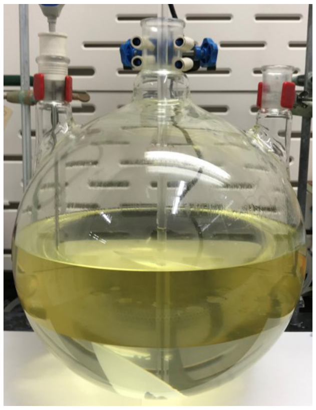
Scalability

While scaling up, there are many issues to consider: cycle times; mixing rates; heat transfer and energy balancing; equipment and utility costs; raw material availability; waste management; and labor are some of the factors that must be thoroughly evaluated when moving from the lab to plant production. For drug sponsors and developers, method selection and scale up should be considered and planned early in the development cycle. There is considerable risk of failure and delay when upscaling a process from early- to late-stage development and later to commercial scale. Many concerns emerge when managing large-scale synthesis, which include safety, quality, and economics. As an alternative to the traditional chemistry found in LPPS and SPPS, GAPPS (Group Assisted Purification Peptide Synthesis) shows great promise for addressing large-scale challenges.

GAP Peptides has recently completed early-stage research to examine the quality, economics, and risks associated with scaling up GAPPS. Herein are some of the findings revealed in the investigation and will be discussed in more detail during our upcoming presentation at the TIDES: Oligonucleotide and Peptide Therapeutics 2020 conference.

Mixing and Equipment Requirements

One of the major challenges with scaling a SPPS process is the heterogenous nature of the reaction mixture. This adds several requirements to the needed process equipment, such as special mixers and filters. And these place limitations on scale. In contrast, GAPPS is a homogenous solution-phase process and therefore does not suffer the same scale limitations. Using GAPPS, reaction mixing is much easier and does not require the special reactors needed for SPPS.



GAPPS on a 100-gram scale in GAP Peptides' lab. Flask size is 12 liters with 4 liters of organic solvent and 3 liters of aqueous wash. Separation is clean and rapid. Scale-up does not require specialized equipment, allows in-process analytics, and reduces process hazards through green chemistry.

Throughput

Process throughput is a critical factor to consider during cale-up. The GAP anchor molecule's small size translates to high peptide loading, > 3 mmol / g. This, along with high reaction concentration (9 – 13 mL solvent / g protected peptide) allows more peptide to be synthesized in the same volume. It also drastically reduces solvent consumption, cutting organic waste streams during synthesis by up to 80% and positively impacting waste management. GAPPS also exhibits efficiency in process time: aqueous extraction requires 1 – 2 minutes for mixing, and phase separation between the 2-MeTHF and water bilayer takes < 2 min even on a 4-liter scale. This compares favorably with the time needed for SPPS solvent addition, mixing, and filtration on similar scales.

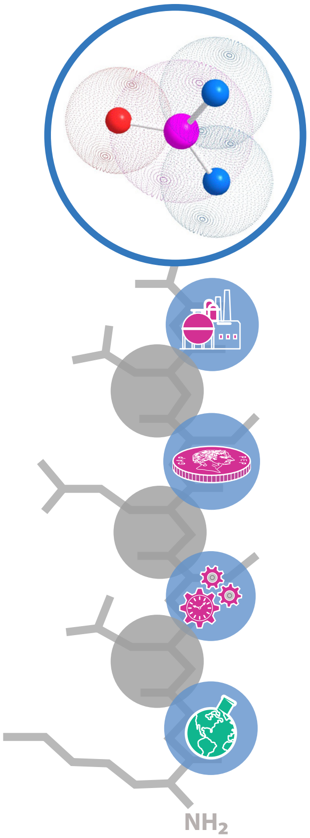
In Process Controls

For any on-scale manufacturing process, in-process controls are critical to ensure the integrity of the batch. GAPPS allows for direct monitoring via HPLC, MS, or 31P NMR at any point of the process. Increased overall cycle times must also be considered, and the process must be robust enough to handle equipment limitations on scale while allowing time for in-process checks to occur. GAPPS allows for coupling reactions to complete in as little as 30 minutes with room-temperature stability for > 8 hours; de-protection reactions also complete in 30 minutes or less and are stable for at least 2 hours. This allows sufficient time for the process and for inprocess analytics to provide results before continuing the synthesis. Also, GAPPS uses standard Fmoc amino acids. While helping from a procurement standpoint, this provides a baseline of familiarity when developing analytical methods.

Conclusion

GAPPS was designed with the concerns of scale-up in mind. By easing the headache involved in process scale-up early on, GAPPS has the opportunity to make a positive impact on product development cycles well before commercial production stage.

GAP Peptide Synthesis: 4 Advantages Over Solid-Phase Synthesis



GAP Anchor Molecule

Enables liquid phase synthesis and Group Assisted Purification

Scalable

Homogenous GAP-PS chemistry does not require specialized reactors or equipment.

Economical

GAP-PS reduces material costs by 50%, while improving peptide yield over SPPS.

Efficient

GAP-PS increases reaction efficiency and delivers high crude purity.

Green

GAP-PS uses green chemistry, reduces solvent waste by 80%, and enables recycling.

To learn more about GAP Peptides' research and collaborative approach to licensing GAPPS technology, visit our website at www.GAPPeptides.com or email Dr. Cole Seifert at cseifert@gappeptides.com

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