Innovations by PeptiStar for Middle-molecule Drug Substance Manufacturing

Introduction

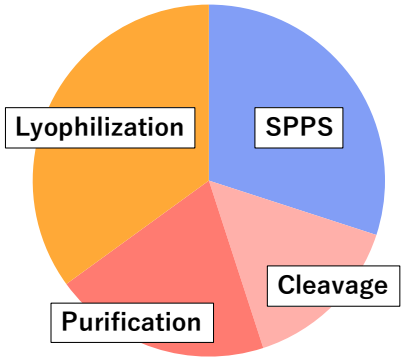

Fig. 1 Processing time in peptide manufacturing

PeptiStar Inc. was established as a peptide CDMO in September 2017 with the head office and factory located in Osaka, Japan. The R&D building and manufacturing workshops started operations in 2019. Thus far, more than 100 research-level samples (10 mg to 10 g), 30 batches of non-GMP products (10 g to 1 kg) and 10 batches of GMP products for early to late phase use have been supplied by PeptiStar.

PeptiStar's peptide synthesis technologies were introduced in the last TIDES featured article published in June 2021. However, the development of peptide synthesis technology alone is not sufficient to rapidly manufacture high-quality peptide drug substances at reasonable costs. Most of the manufacturing cost comes from processing (though it depends on the type of special amino acid, etc.), which in turn can be rephrased as processing time. As shown in Fig. 1, the synthesis accounts for only about ¼ of the total processing time in peptide manufacturing, so to drastically reduce the manufacturing cost, it could be achieved by shortening the processing time of all four steps.

1. A Series of The World's First Technologies in Peptide Manufacturing

PeptiStar has been working on developing technology in all the steps of peptide manufacturing to shorten manufacturing time and reduce manufacturing cost.

In cooperation with its partners, PeptiStar identifies problems in manufacturing processes and makes technological innovations to overcome those problems. In the TIDES June edition, PeptiStar introduced the microwave solid phase synthesis and STag-PS™ synthesis technology. In addition, PeptiStar also utilizes other technologies such as SYNCSOL™ (discussed later in this article), continuous chromatography, and application of HILIC for purification, as well as new membrane concentration method and new freeze-drying method replacing tray dryer (discussed later in this article). Fig. 2 shows a series of technological innovations for peptide manufacturing that PeptiStar is working on.

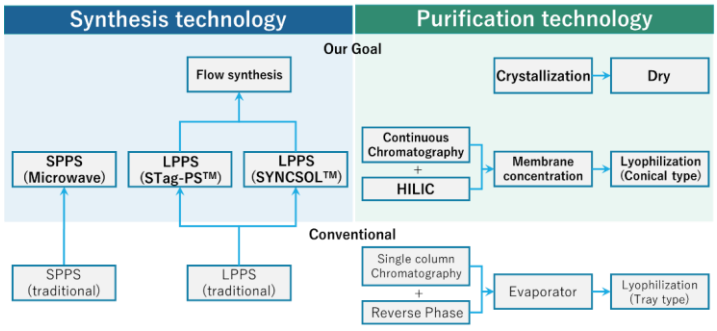

Fig.2: A series of innovative peptide manufacturing technologies being developed by PeptiStar

SYNCSOL™ (developed with PeptiDream Inc. and Nissan Chemical Corporation)

SYNCSOL™ (Fig. 3) developed by Nissan Chemical Corporation and PeptiDream Inc. is a very unique liquid phase peptide synthesis technology platform utilizing silyl protection technology (SIPS™) and unprotected amino acid coupling technology (R-Coupling™).

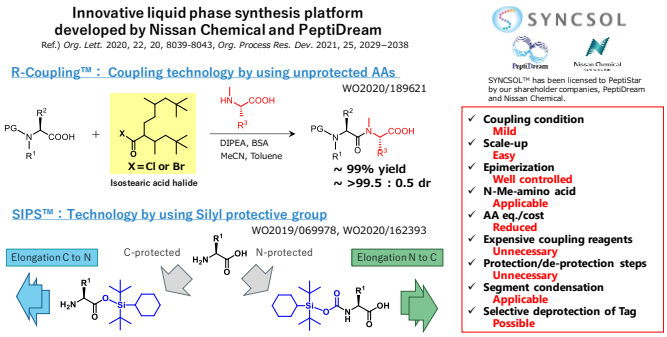

Fig.3 Conceptual Diagram of SYNCSOL™

In conventional solid phase synthesis, an Fmoc protected amino acid is supported on the solid phase and the peptide chain is extended from the C-terminus by adding Fmoc protected amino acids in sequential order. R-Coupling™ is a peptide synthesis technology which extends the amino acid from the N-terminus using an unprotected amino acid. This method enables drastic reduction in raw material cost by using an amino acid without a protecting group, contributing to the reduction of processing time since the deprotection process for every condensation step is not necessary.

SIPS™ is the technology which suppresses the side reaction by protecting the C-terminus or N-terminus with a silyl group, acquiring a high-quality peptide intermediate by only using liquid separation or crystallization.

By using this platform, PeptiStar. succeeded in significantly reducing raw material costs compared to solid phase synthesis and the purification load was reduced by improving the quality of the crude peptide.

Continuous Chromatography (developed with YMC Co., Ltd.)

Purification is an important step in determining the quality of the peptide. Usually, the quality of the target drug substance coincides inversely with the recovery rate. However, if we use continuous chromatography (Fig. 4), the technology makes it possible to obtain a high-quality drug substance, while maintaining a high recovery rate. This type of chromatography is also useful for quality design strategy in which quality needs to be improved according to the phases of development. Since high quality and high recovery rate can be simultaneously achieved, we can reduce the synthesis scale relative to the target quantity, contributing to the drastic reduction in raw material cost.

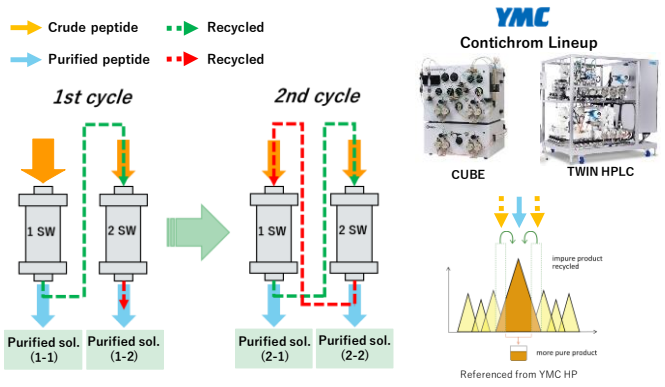

Fig.4 Conceptual Diagram of Continuous Chromatography

New Membrane Concentration Method (developed with Asahi Kasei Co., Ltd.)

After the purification process, the purified solution is lyophilized to isolate the peptide as solid. Depending on the volume of the solution, lyophilization is required multiple times, which increases manufacturing time. Vacuum concentration may be applied to reduce the liquid volume, but peptides are usually vulnerable to heat. Therefore, PeptiStar developed a new membrane concentration method with Asahi Kasei Co., Ltd. (Fig. 5). The conventional membrane concentration method can concentrate a solution without a heat load, but it is not easy to control the solution composition. For example, poorly soluble peptides often precipitate during concentration, thus the conventional membrane concentration method cannot be applied. However, this new membrane concentration method makes it possible to control the solution composition without incorporating heat or pressure. With this method, we can reduce the number of cycles of lyophilization, which means that the manufacturing time can also be shortened.

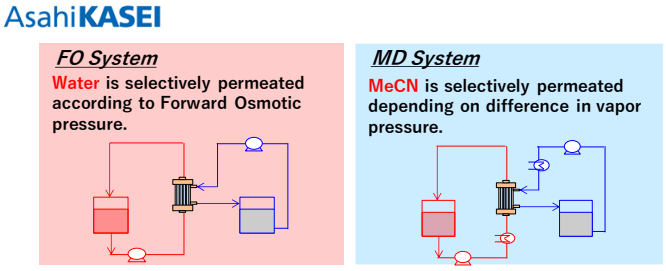

Fig. 5 Conceptual diagram of the new membrane concentration method

New Freeze-Drying Method (developed with KOBELCO ECO-SOLUTIONS Co., Ltd.)

The freeze-drying process is generally very time-consuming. Besides that, there is also a problem with homogeneity between trays in tray dryers. However, with our new freeze-drying method, the manufacturing time can be reduced over 80% compared to the conventional method and the homogeneity issue can also be resolved (Fig. 6).

By making all the innovations in each step of the process introduced above, PeptiStar is able to manufacture high quality peptide drug substances at reasonable prices.

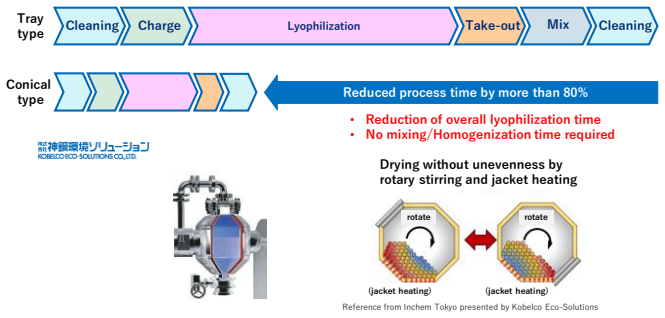

Fig.6 Conceptual Diagram of New Freeze-Drying Method

In the next article to be featured in the TIDES March 2022 edition, we are planning to present the actual data on our technology development.

2. Oligonucleotide Manufacturing

Recently, development of drugs using middle molecules is getting attention in the industry, but structures are also getting more and more complex. Peptide drugs also have some variations of conjugation such as with PEG, antibodies, and oligonucleotides. Therefore, pharmaceutical companies need to work with oligonucleotide CDMOs separate with peptide CDMOs, which makes procurement time-consuming. PeptiStar started contract manufacturing of oligonucleotides in 2021 utilizing its know-how acquired through peptide manufacturing. PeptiStar will start its operations at a manufacturing facility for oligonucleotides in the summer of 2022 with the ability to produce several hundred grams of GMP batches (Fig.7).

With this new manufacturing capability, peptides, oligonucleotides, and their conjugates can be produced by PeptiStar, increasing efficiencies in communication and lead time for procuring middle-molecule drug substances (Fig. 8). Additionally, PeptiStar can also utilize the same technologies in manufacturing oligonucleotides and peptides for downstream process from purification. Therefore,

PeptiStar can rapidly manufacture high quality oligonucleotides at reasonable costs.

PeptiStar will continue to work diligently on the further development of drugs using middle molecules.

Fig. 7 PeptiStar production facilities

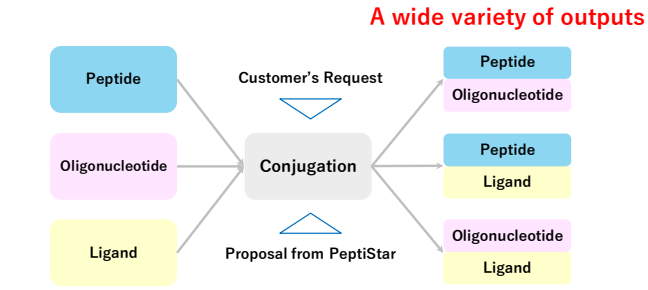

Fig. 8 PeptiStar's Role

(Contact Information)

PeptiStar Inc.

PeptiStar HP: https://PeptiStar.com/

Contact：y-watanabe@PeptiStar.co.jp

Yasumasa Watanabe

Vice President,

Corporate Strategy Department (Marketing Responsible)