Development of Next Generation Processes for Drug Substance Manufacturing Utilizing Continuous Manufacturing Technology

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Continuous manufacturing technology has been attracting increasing attention in the pharmaceutical drug substances (DS), development field. While continuous techniques are being utilized in various unit operations of DS manufacturing, application of continuous manufacturing technology to the chemical synthesis step, also known as flow chemistry, can the potentially to enable the development of highly productive manufacturing processes that were not possible with conventional batch-type reactors alone.

We herein, we introduce a case study in which continuous manufacturing technology was utilized to develop a manufacturing process for EPI-589, a current drug candidates in our small molecule pipeline.

Introduction

Medicines administered to treat specific diseases are formulated so that the active pharmaceutical ingredient (API) can act in the body both effectively and safely. The quality design of the API and its formulations, establishment of manufacturing methods, and preparation of approval applications are collectively referred to as chemistry, manufacturing, and controls (CMC) research. Such research must consider not only product quality but also cost and safety. For instance, the API (small molecule) manufacturing process typically involves the following unit operations: (1) preparation, (2) reaction, (3) extraction, (4) concentration, (5) crystallization, (6) filtration, (7) drying, and (8) milling. Optimizing these unit operations represents an important aspect of CMC research. In recent years, there has been a growing trend toward applying "continuous manufacturing technology" (CMT) to these unit operations, and commercial-scale production using such methods has been progressing (**Fig. 1**).

CMT differs from conventional batch manufacturing in that reactions and other unit operations are performed seamlessly within a microscopic space. Employing this technology offers the potential for substantial benefits in terms of safety, quality, and cost efficiency. In particular, in drug-discovery manufacturing, CMT exerts the greatest influence on the (2) reaction and (5) crystallization unit operations. CMT for the (2) reaction unit operation, which is also known as "flow synthesis" or "flow chemistry," has been extensively studied by industry, government, and academia[1]. It should be noted that there are significant differences between the CMT process-development approaches for APIs and their formulations.

As an additional note, Sumitomo Chemical Co., Ltd. was among the first companies in Japan to recognize the advantages of flow-synthesis technology, as highlighted in a previous publication[2]. Moreover, in 1996, the "Flow Microsynthesis Study Group"[3] was established within the Kinki Chemical Society to promote collaboration among industry, government, and academia on this technology. The Dohgane Award is presented to researchers who have produced exceptional achievements. This award was named

* Retired at the time of publication.

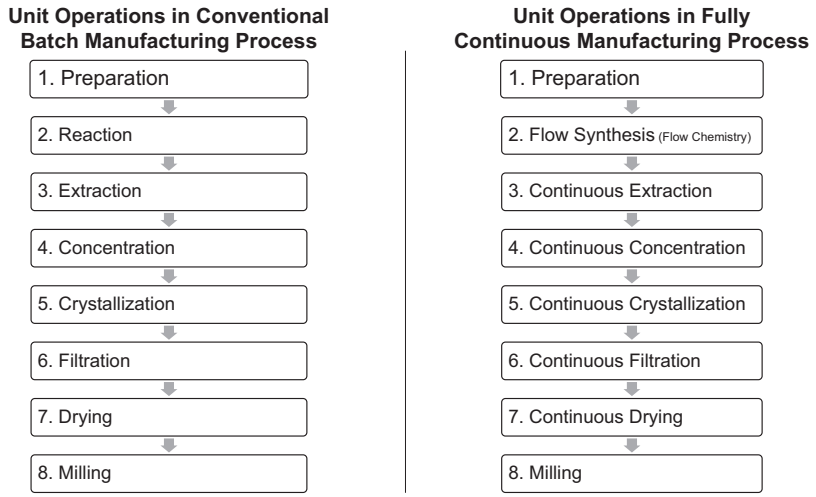
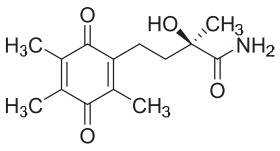


Fig. 1 Continuous manufacturing applied to small molecules in the pharmaceutical industry

in honor of Iwao Dohgane, a former Director of the Sumitomo Chemical Industry Co., Ltd. Organic Synthesis Research Laboratory and former President and CEO of Sumika Technical Information Service, Inc., who played a key role in forming this study group. The Sumitomo Chemical Group takes great pride in having been an early adopter of this technology.

These trends show that CMT and flow synthesis have been gaining widespread attention. Therefore, in this article, we introduce an example of how CMT has been applied to develop manufacturing processes for APIs, using the case of the small-molecule compound EPI-589.



(*R*)-Troloxamide Quinone
EPI-589

Fig. 2 Chemical structure of EPI-589

About EPI-589

Many pharmaceutical companies are actively developing pharmaceuticals aimed at curing or alleviating neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (ALS). EPI-589 is one of these pharmaceutical candidates. It is a small-molecule compound designed and developed by Edison Pharmaceuticals, Inc. (now PTC Therapeutics) in the United States and licensed to Sumitomo Dainippon Pharma Co., Ltd. (now Sumitomo Pharma Corp.) through a licensing agreement. **Fig. 2** shows its chemical structure.

The first-generation manufacturing process for EPI-589 was designed based on the synthesis route shown in **Fig. 3**, but it encountered two major challenges,

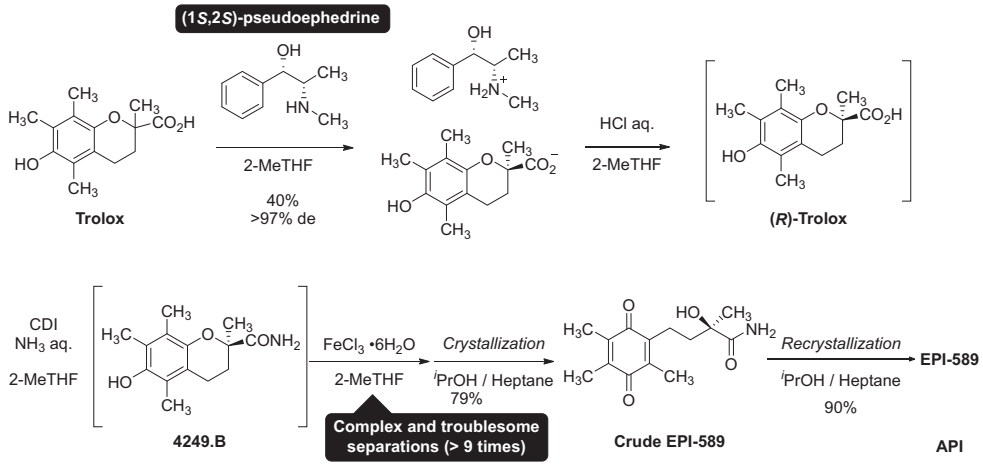


Fig. 3 First generation process for EPI-589 synthesis

which were as follows.

1) The use of (1*S*,2*S*)-pseudoephedrine as a resolving agent: This compound serves as a raw material for stimulants, and its use is restricted in Japan and numerous other countries.
2) Numerous separation and purification steps in the oxidation reaction: The oxidation reaction using iron(III) chloride necessitated over nine separation and purification steps, which posed a serious challenge to productivity.

To overcome these challenges, we began investigating resolving agents to replace (1*S*,2*S*)-pseudoephedrine, along with process improvements for the oxidation reaction.

Development of a second-generation manufacturing process for EPI-589

In response to the above-mentioned challenges, our Process Chemistry Division conducted manufacturing studies and successfully established the following second-generation manufacturing process (**Fig. 4**).

In this new manufacturing process, (*R*)-1-phenylethylamine (henceforth, "(*R*)-PEA") was used as the resolving agent instead of (1*S*,2*S*)-pseudoephedrine. We also replaced iron(III) chloride hexahydrate with iron(III) nitrate nonahydrate as the oxidizing agent. As a result, we substantially reduced the number of separation and purification steps (from nine in the first-generation process to four in the second-generation process). Notably, we discovered a novel optical-resolution phenomenon during the optical-resolution process. We incorporated this discovery into the manufacturing process, thereby successfully developing a practical manufacturing process. Specifically, the desired stereoisomer (*R*)-Trolox and (*R*)-PEA formed a salt, and N-methylpyrrolidone (NMP) also coordinated with the compound, resulting in a ternary complex salt and stable optical resolution (**Fig. 5**). Ordinarily, NMP is a highly soluble solvent and is generally avoided, particularly in optical-resolution procedures. However, in this case, the low solubility of the NMP complex salt enabled isolation and purification through crystallization.

Prior to the identification of a stable optical resolution through the NMP complex salt, (*R*)-Trolox could not be obtained using (*R*)-PEA during crystallization, and only the racemic Trolox was recovered as crystals. X-ray crystallography analysis of the resulting racemic crystals revealed the structure illustrated in **Fig. 6**.

Figs. 5 and **6** show that (*R*)-PEA forms salts with both the (*R*) and (*S*) forms of Trolox. Furthermore, the carboxyl group of (*R*)-Trolox and phenolic hydroxyl group of (*S*)-Trolox interact via hydrogen bonds, leading to the precipitation of (*R*)-Trolox, (*S*)-Trolox, and 2 (*R*)-PEA (racemate). NMP prevents this hydrogen-bonded association by forming a salt as a solvate, which results in the stable precipitation of (*R*)-Trolox, (*R*)-PEA, and NMP, allowing a reproducible optical resolution. The development of this three-component optical-resolution method represents a highly innovative technique from a scientific standpoint.

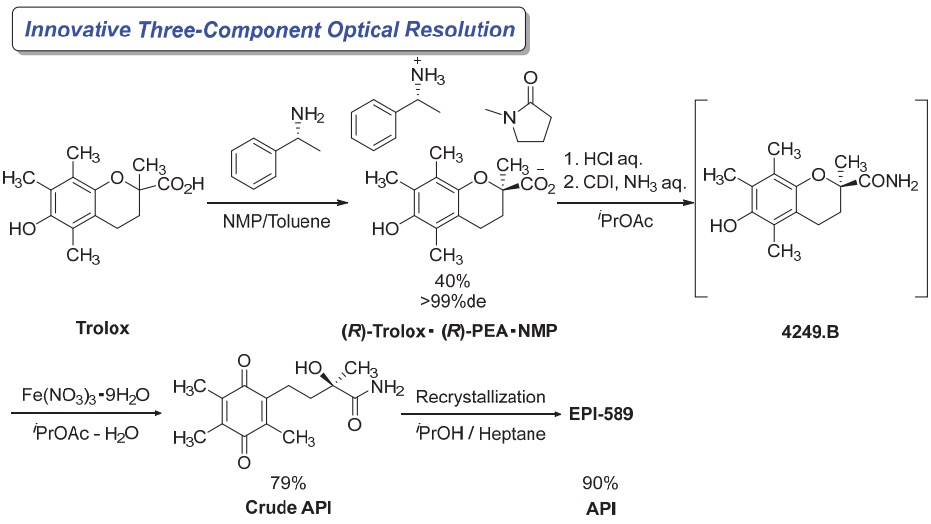


Fig. 4 Second generation process for EPI-589

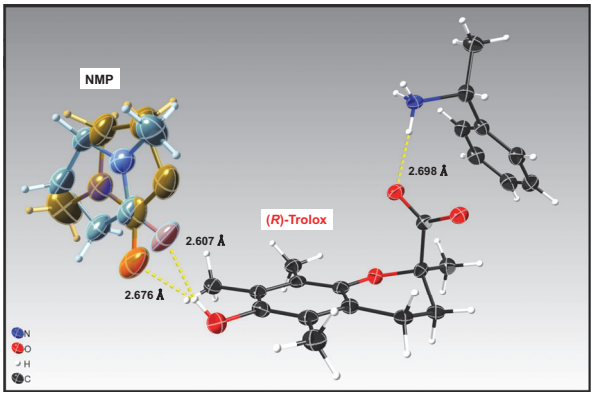


Fig. 5 X-ray crystal structure analysis of (*R*)-Trolox revealed the association of NMP and (*R*)-PEA

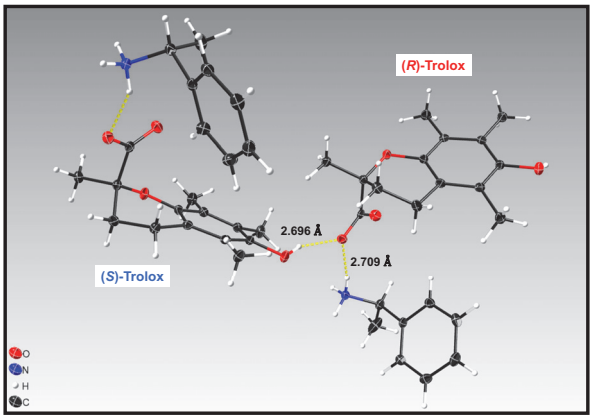


Fig. 6 X-ray crystal structure analysis of the obtained racemate

New challenges with second-generation manufacturing process (nitrosamine formation and contamination)

The second-generation manufacturing process described in the previous section can be implemented without issues even at scales exceeding 80 kg and has been established as an excellent, highly reproducible process. However, although the Pharmaceuticals and Medical Devices Agency (PMDA) later issued the guideline "Evaluation and Control of DNA-Reactive (Mutagenic) Impurities in Pharmaceuticals to Reduce Potential Carcinogenic Risk" (ICH M7)[4], at the early stage of this program's development, the regulatory concept for evaluating and controlling contamination by nitrosamine, which was considered more carcinogenic, had not yet been fully established. Therefore, the EPI-589 produced using the second-generation process was also evaluated for nitrosamine formation and contamination risk as described below.

The second-generation manufacturing process for EPI-589 employs NMP and iron(III) nitrate. Although these two compounds are not used in equivalent quantities within the same process step, residual NMP from the optical-resolution process may carry over to downstream steps, where it could react with the nitrite ions present in the iron(III) nitrate used in the oxidation reaction, leading to the formation of the nitrosamine *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA) (**Fig. 7**).

Based on this risk assessment, we quantified the NMBA content in the EPI-589 manufactured using the second-generation process and detected NMBA in the API, although its concentration was below the limit of quantitation (less than 5 ppm).

The acceptable intake level of NMBA has been estimated to be 96.0 ng/day[5]. From a toxicological perspective, it would have been theoretically feasible to continue development while carefully evaluating the contamination levels. Nonetheless, given the expected long-term continuous administration of this drug to patients with Parkinson's disease and ALS, we concluded that the risk of NMBA contamination should be completely eliminated and chose to further improve the manufacturing process.

Development of third-generation manufacturing process for EPI-589

(1) Reverting to the iron(III) chloride method

As described earlier, the second-generation manufacturing process led to the development of an excellent new optical-resolution method. However, it was found that the NMP coexisting with the solvated crystals could react with nitrite ions originating from the iron(III) nitrate used in subsequent steps, causing

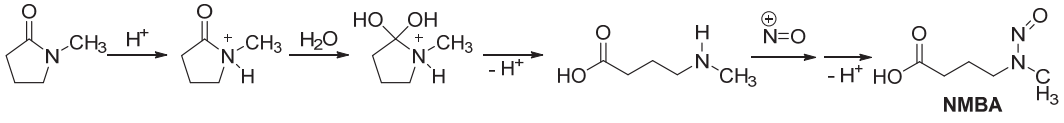


Fig. 7 Proposed route to NMBA from NMP

nitrosation and contamination (NMBA). When considering the entire manufacturing process, optical resolution using NMP was found to be excellent in terms of both the yield and reproducibility. Therefore, we decided to leave the optical-resolution step unchanged while improving the oxidation step to prevent contact with nitrite ions. At this point, we revisited the first-generation manufacturing process. In the first generation process, iron(III) chloride was employed as the oxidizing agent. As previously mentioned, this oxidation required more than nine analytical steps during manufacture. The main reasons for this are outlined below.

When the final intermediate (4249.B) dissolved in the organic layer came into contact with an aqueous iron(III) chloride solution and separated to promote oxidation, the addition and separation of this aqueous iron(III) chloride solution had to be repeated at least four times.

Moreover, unreacted iron(III) chloride and by-products such as iron(II) chloride and hydrochloric acid generated after oxidation had to be removed, and multiple neutralization, separation, and purification steps were required to remove these inorganic materials.

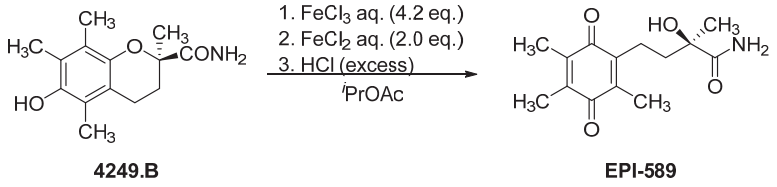
Although this oxidation reaction necessitated at least four iterative analyses, our group suspected that it might be an equilibrium reaction and performed the following verification experiment (**Fig. 8**).

When 4249.B in isopropyl acetate solution was oxidized with iron(III) chloride (Entry 1), the subsequent addition of iron(II) chloride caused a slight regeneration of the raw material, 4249.B (Entry 2). More interestingly, when excess hydrochloric acid was introduced into the reaction mixture, the reverse reaction proceeded and produced 4249.B at an area percentage of 26.4% (Entry 3). This observation strongly suggested that the oxidation reaction was an equilibrium process, as illustrated in **Scheme 1**.

Focusing on this equilibrium behavior, we hypothesized that by shifting the equilibrium to the product side, the reaction could be accelerated and the numerous separation steps used in the first-generation process could be reduced. Specifically, we theorized that adding a base during the reaction would capture the hydrochloric acid formed and thereby drive the equilibrium to the product side. Through various experiments, we found that introducing 2.1 equivalents of a base (aqueous sodium hydroxide solution) shifted the reaction to the product side and enabled the efficient formation of the desired EPI-589 (**Scheme 2**).

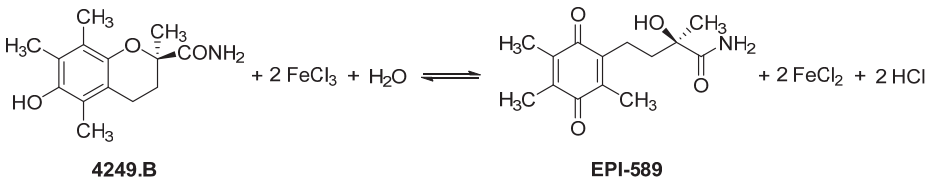
(2) Challenges with iron(III) chloride method and flow-synthesis technology

As explained in the previous section, the addition

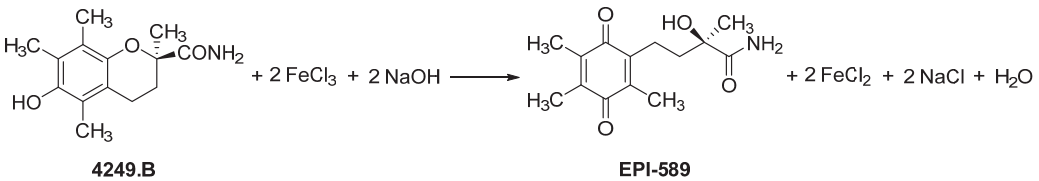


Entry	Timing of Analysis	HPLC area%	
		4249.B	EPI-589
1	After adding $FeCl_3$	0.0	79.2
2	After adding $FeCl_2$	0.2	78.1
3	After adding HCl	26.4	57.4

Fig. 8 Confirmation of Reduction after Oxidation



Scheme 1 The oxidation reaction of 4249.B as an equilibrium reaction



Scheme 2 Accelerating oxidation of 4249.B to EPI-589 by $FeCl_3$ & base

Fig. 9 Solidification of the reaction mixture during the oxidation step

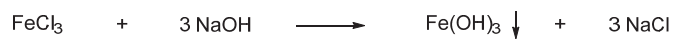
of a base to the oxidation using iron(III) chloride was shown to move the equilibrium toward the product side. However, this approach also presented one major challenge. During this reaction, the introduction of a base produced a slurry, and depending on the timing of its addition, solidification could occur inside the reactor, as shown in **Fig. 9**.

If a typical manufacturing reactor experiences the situation shown in **Fig. 9**, it becomes extremely difficult to remove the contents, and in the worst case, the reactor might need to be destroyed. Therefore, the timing of the base addition was considered critical, and we examined various reaction conditions. Even when bases other than sodium hydroxide were tested, solidification still occurred.

In this reaction, hydrochloric acid is generated quantitatively as the oxidation with iron(III) chloride progresses. Neutralizing this hydrochloric acid with a base shifts the equilibrium reaction toward the product side. However, the timing of the base addition is critical. If it is added too early or too late, insufficient hydrochloric acid may be captured. In such cases, unreacted iron(III) chloride reacts with the aqueous sodium hydroxide, producing a precipitate, as shown in **Scheme 3**. This obstructs the desired oxidation reaction and complicates the removal of the product from the reactor.

Based on these observations, we decided to focus our research on developing a process in which iron(III) chloride reacts at the optimal time, with sodium hydroxide added at precise intervals. Flow-synthesis technology is particularly well-suited for controlling both the timing and mixing with high precision. Therefore, we carried out a series of studies using flow-synthesis technologies and ultimately determined that the oxidation reaction could proceed quantitatively and consistently under the following conditions (**Figs. 10** and **11**).

Specifically, 4249.B was prepared as a 0.5 M solution in dimethyl sulfoxide (DMSO), with a 4 mol/L aqueous solution of iron(III) chloride prepared separately. These solutions were delivered at flow rates of 10 and 5.25 mL/min, respectively, and combined in the first mixer, which had an internal diameter of 0.5 mm. The mixed solution then flowed through a 25-cm-long tube with an internal diameter of 1 mm, giving a residence time of 0.77 s, after which it was combined with a 5.0 mol/L aqueous sodium hydroxide



Scheme 3 Side reaction of $FeCl_3$ with Base (NaOH)

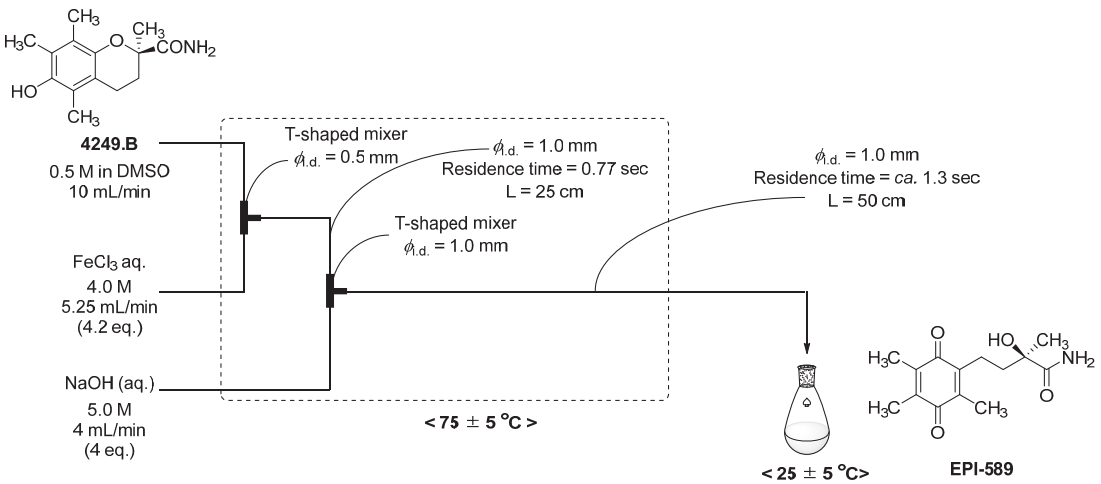


Fig. 10 Flow system of the oxidation step

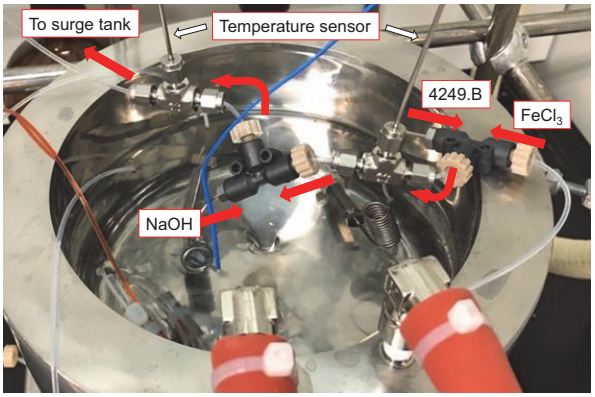


Fig. 11 Flow reactor for the oxidation step

solution in the second mixer, which had an internal diameter of 1.0 mm. Finally, the reaction mixture was collected in a flask. Under these conditions, the solution exiting the flow reactor remained a slurry that could be stirred, confirming the progress of a stable reaction. After reaching the reaction endpoint, the mixture was post-treated by adding water or a small amount of acid to dissolve all of the inorganic salts. This allowed a state in which only EPI-589 crystals were stirred in the solution, enabling the selective isolation and acquisition of EPI-589 by simple filtration. This approach is here referred to as the third-generation manufacturing process. **Fig. 12** shows a comparison of the first-generation (original process) and third-generation processes. Ultimately, the nine separation and purification steps were entirely eliminated. We also found that high-quality EPI-589 could be obtained merely by adding hydrochloric acid and water to the solution after the flow reaction to dissolve inorganic salts. Furthermore, this method facilitated the establishment of a process that theoretically does not generate nitrosamines (NMBA).

Building on these lab-scale studies, multi-kilogram demonstration experiments and their extension to GMP manufacturing are described below.

(3) Scaling up the third-generation manufacturing process

The previous section discussed how we designed an EPI-589 manufacturing process using flow synthesis with iron(III) chloride as the oxidizing agent. However, all of the prior studies were conducted on the gram scale (small scale). Therefore, before implementing GMP manufacturing using this manufacturing process, we performed non-GMP production on a multi-kilogram scale to demonstrate the CMT.

This manufacturing process involves a reaction that produces a slurry. Therefore, the internal diameter of the flow reactor was enlarged to 10 mm to prevent blockage. The linear velocity used in the lab-scale study was maintained, but the raw-material feed rate was increased 100-fold (**Figs. 13**, **14**, **15**, and **16**). In this demonstration, the flow reactor was connected to a mixer and tubing made of PFA, which is a fluororesin material. As a result, continuous operation was successfully maintained for 2 h, with the manufacture completed without any blockage.

Based on these results, we concluded that a further scale-up was feasible using the basic design of the flow reactor, and we proceeded with GMP manufacturing.

(4) GMP manufacturing using third-generation manufacturing process

GMP manufacturing of this developed compound was conducted in collaboration with Hamari Chemicals,

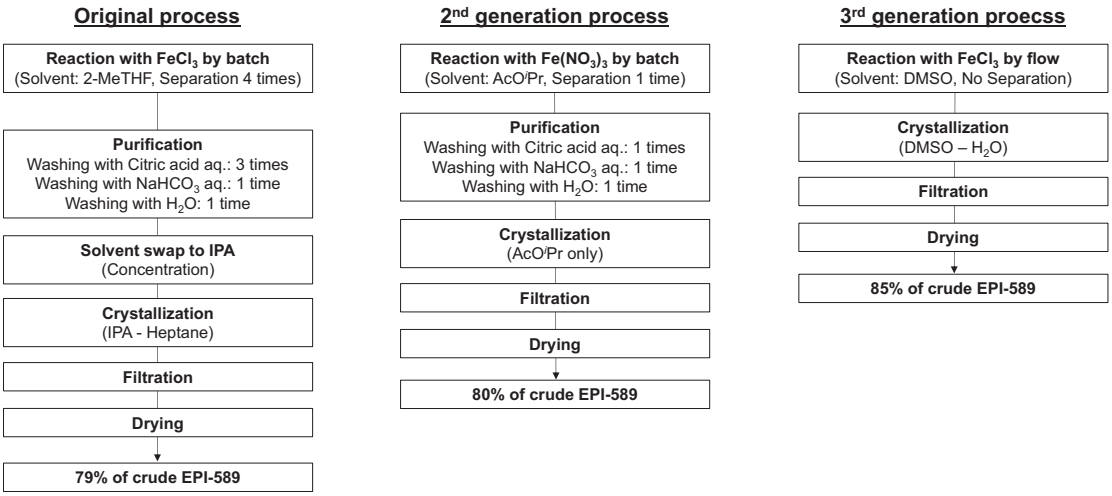


Fig. 12 Comparison of the oxidation step in the original, 2nd & 3rd Processes

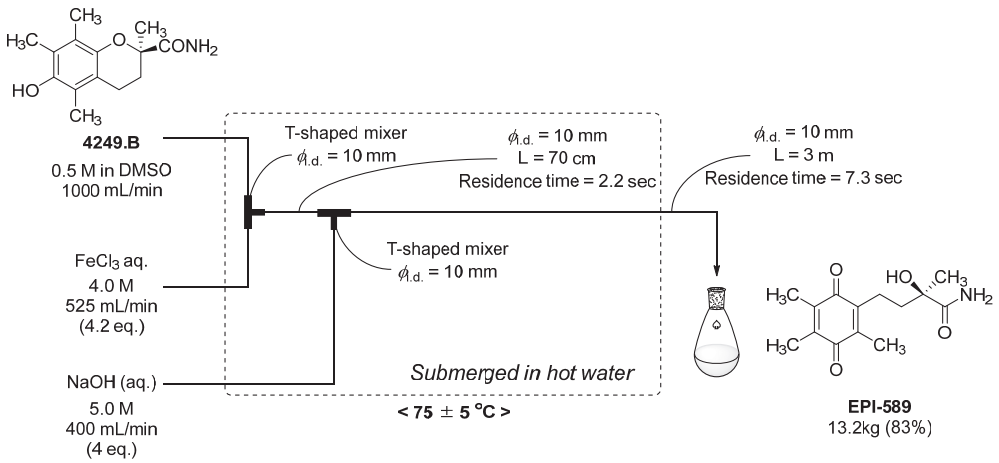


Fig. 13 Multi-kg Scale Manufacturing using a PFA Flow Reactor (Operation Time: 2 hours)

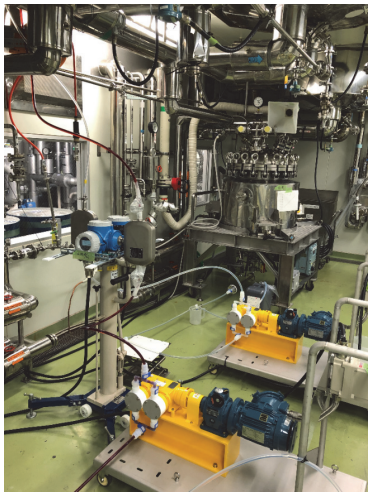


Fig. 14 TACMINA, PL series pump (PLFYD2-1-TTXX-FWX-A32)

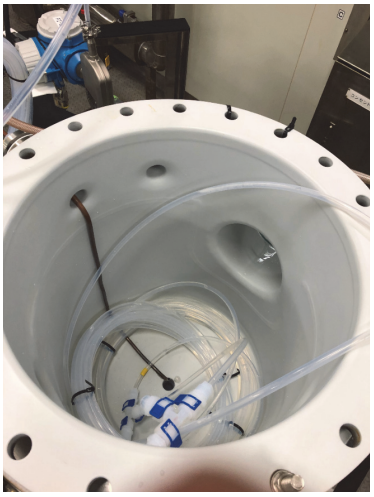


Fig. 15 Inside the installation bath for the flow reactor

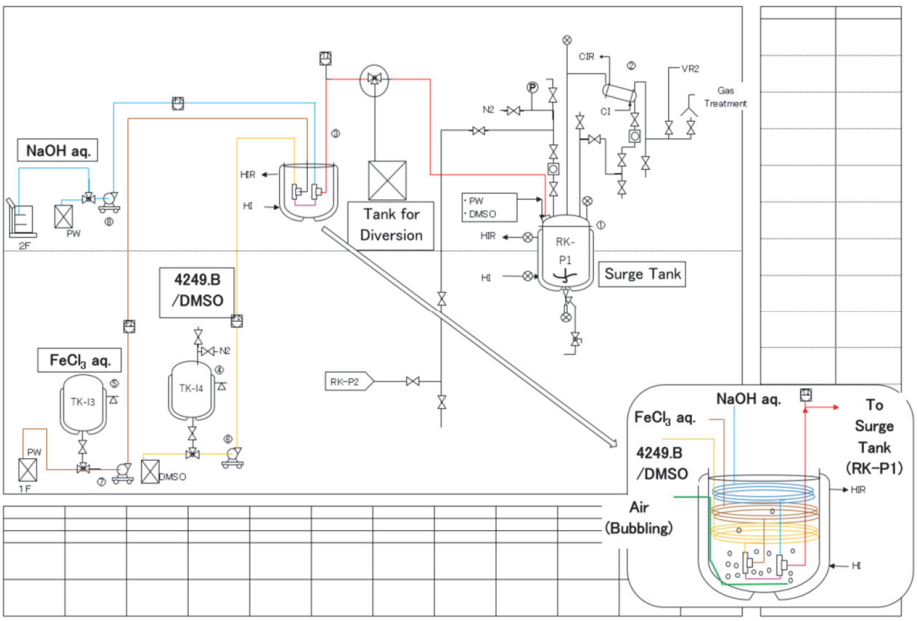


Fig. 16 Blueprint of flow reactor for EPI-589 non-GMP manufacturing

Ltd. and its affiliate, Hamari PFST Co., Ltd. The above-mentioned non-GMP production was conducted at our facilities with PFA flow-reactor components. For GMP manufacturing, the equipment was constructed with assistance from Hokusetsu Kakoki Seisakusho Co., Ltd. using a corrosion- and heat-resistant alloy (**Fig. 17**).

We employed the same Tacmina Corp. PL series pump (PLFYD2-1-TTXX-FWX-A32, **Fig. 14**) for precise flow control as used in the non-GMP manufacturing, along with a Proline Promass A 300 Coriolis flow meter from Endress+Hauser Japan (**Fig. 18**).

In implementing the GMP manufacturing, we coordinated with stakeholders to define lots and other details, referencing the ICH Harmonized Guidelines for Continuous Manufacturing of Drug Substances and Drug Products (ICH Q13, step [4),6)] at the time), before commencing production. Manufacturing instructions were created to specify that each lot would undergo continuous operation for approximately 9–13 h, depending on the capacity (size) of the reactor receiving the flow-reactor discharge-solution output, and manufacturing was conducted in three lots.

As shown in **Fig. 19**, crude EPI-589 API quantities of 58.0, 74.2, and 88.3 kg were obtained. These were subsequently subjected to the final process (recrystallization) to yield the API without any quality issues in all cases.

Summary of development of third-generation manufacturing process

As outlined above, during the development of the EPI-589 manufacturing process, we established a novel optical-resolution approach based on the discovery of a ternary complex salt. Additionally, to mitigate the nitrosamine (NMBA) risk, the oxidizing agent was switched to iron(III) chloride. To address the potential reaction-termination risk, the conventional batch reactor was converted to a flow reactor, which resulted in a manufacturing method utilizing CMT[7)]. Although this approach successfully produced over 200 kg of the target product, which indicated its high commercial potential, the program was discontinued as a result of portfolio-related strategic decisions.

Fig. 17 corrosion-resistant and heat-resistant alloy flow reactor (inner diameter 10 mm)

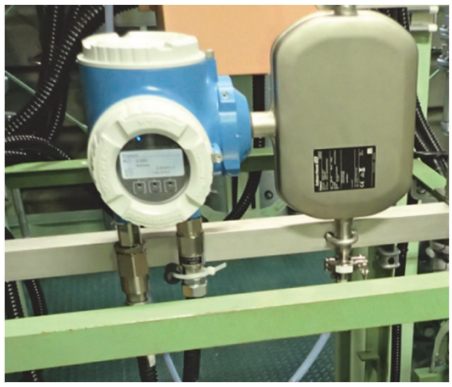


Fig. 18 Endress+Hauser, Proline Promass A 300, coriolis flow meter

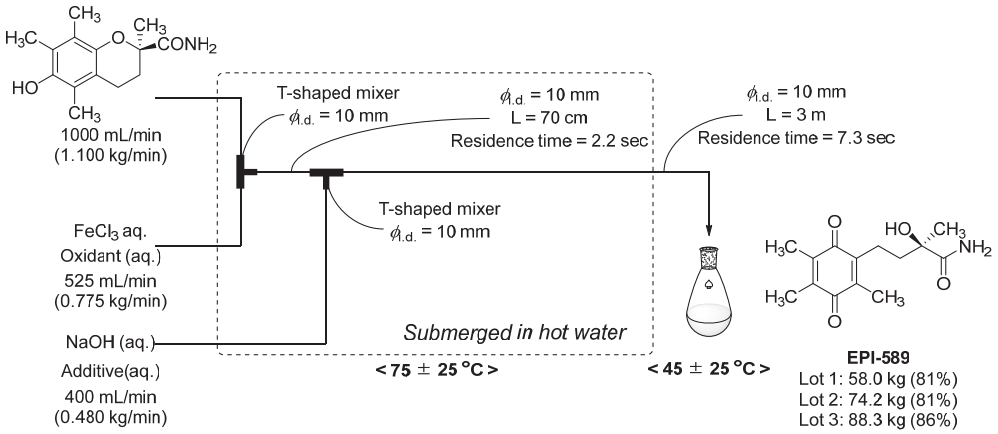


Fig. 19 GMP Manufacturing of the API (EPI-589) using a Flow System

Further prospects

As described, we developed a process suitable for commercial-scale EPI-589 production using the third-generation manufacturing process. Nonetheless, additional improvements were needed to reduce waste, as observed before its discontinuation. While evaluating new technologies for the oxidation process, we considered the potential of electrolytic oxidation, which is a technique that is rarely applied in pharmaceutical synthesis. In fact, applying oxidation to 4249.B using an electrolytic device such as that shown below (IKA ElectraSyn 2.0) at the milligram scale confirmed that an excellent yield of EPI-589 could be obtained (**Fig. 20**, **Scheme 4**).

Because examples of electrochemical process development in the pharmaceutical industry remain scarce, we expect future growth in this area. However, scaling up will require the careful selection of electrodes and electrolytes, control and suppression of side reactions near the electrodes, and design of scalable equipment. Thus, as with any conventional batch reactor scale-up, multiple scale-up factors need to be considered. Nonetheless, combining flow-synthesis technology with an electrolytic oxidation method is expected to facilitate the scale-up of this method.

This electrolytic oxidation + flow synthesis approach was developed in collaboration with Asymchem Laboratories. Following extensive planning, the system shown below was constructed and successfully scaled to 1 kg (**Fig. 21**).

The crude EPI-589 API obtained via this electrolytic oxidation + flow synthesis method can be subjected to a final recrystallization step, similar to the third-generation process, in order to yield a high-quality API (**Scheme 5**).

Fig. 20 Anodic oxidation using an ElectraSyn 2.0 apparatus

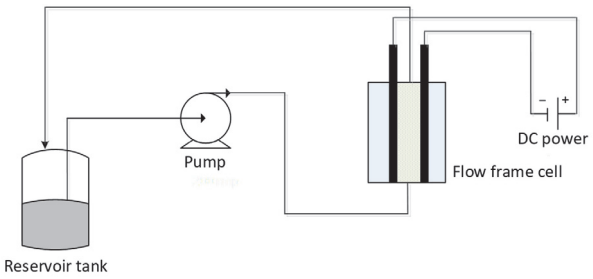
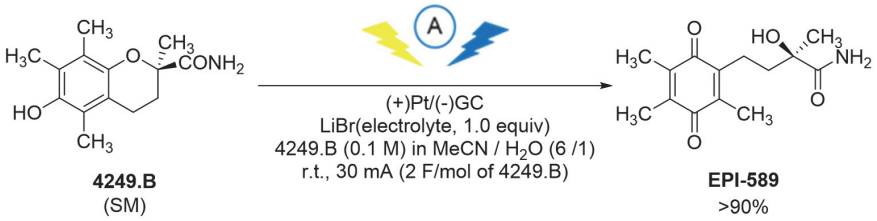
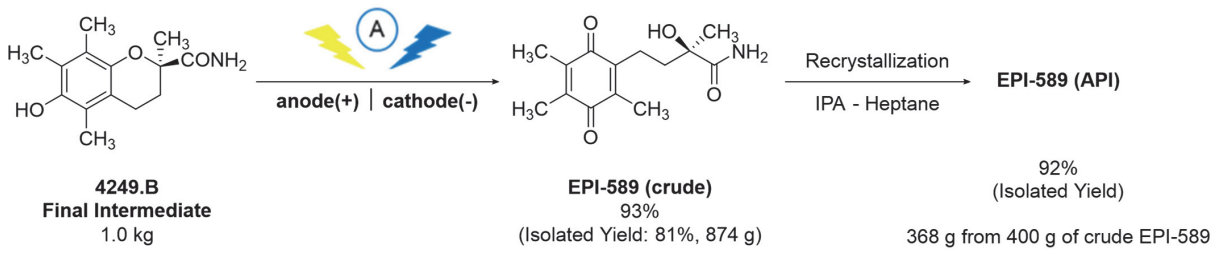


Fig. 21 Set-up of the flow electrochemical reaction using a frame cell



Scheme 4 Feasibility study of the anodic oxidation of 4249.B



Scheme 5 Scale-up and quality confirmation of EPI-589 synthesized by electrochemical process

In production using 1 kg of 4249.B, no blockage occurred even after 17.5 h of continuous operation, demonstrating the feasibility of further scaling up the process[8]. We had intended to submit an application for EPI-589 using a third-generation process and, after market launch, file an application for a partial change to medical device manufacturing and sales approval items (a partial change application) to notify authorities of the manufacturing change. However, as previously mentioned, the development was discontinued, which halted the progress on these electrosynthesis methods.

Conclusion

This article focused on “continuous manufacturing,” which was illustrated using an example of flow-synthesis technology applied to the development of a pharmaceutical process and realization of a manufacturing technology. CMT can overcome challenges that are impossible to overcome with conventional batch reactors alone and is compatible with electrochemical technology, which is a promising future technology. Thus, continuous manufacturing and flow synthesis can enhance productivity and quality, not only in pharmaceutical development but also across diverse chemical-synthesis fields. We anticipate that chemical processes that utilize these technologies will become widely implemented, producing many successful examples.

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