



Review paper

Electrochemical strategies for peptide synthesis, deprotection and scalable reactor technologies

Pradip Mali  and Inkollu Sreedhar  

Department of Chemical Engineering, BITS Pilani Hyderabad Campus, Hyderabad-500078, India

Corresponding Author: ✉ Jsreedhar@hyderabad.bits-pilani.ac.in

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Abstract

Peptides have high target specificity, favourable safety profiles, and increasing applications in oncology, metabolic disorders, infectious diseases, and precision medicine, making them one of the fastest-growing classes of therapeutic molecules. Traditional peptide synthesis involves more hazardous solvents and stoichiometric quantities of coupling reagents, which lead to high process mass intensity and environmental impact. In electrochemical synthesis, electrons are traceless redox reagents that allow for the controlled activation and transformation of peptide substrates under mild conditions. Advances in electrochemical peptide bond formation, electrochemical deprotection methods, and new technologies of electrochemical reactors for peptide synthesis are critically discussed. The focus is on phosphine-mediated anodic peptide coupling, iodide-mediated amide formation, residue-selective electrochemical modifications and redox-triggered deprotection methods. Advances in flow electrochemistry, scalable reactor designs and sustainable peptide production methods are thoroughly discussed. The effect of electrochemical parameters such as the electrode materials, current density, solvent systems, electrolytes, reaction time, and reactor design on reaction efficiency and selectivity is critically evaluated. However, there are still some issues that need to be addressed, such as the scope of the substrates, the lack of understanding of the mechanisms, fouling of the electrodes, scalability and the absence of a standardized method of reporting. Opportunities for the future include the combination of electrochemistry and continuous-flow processing, sustainable solvent systems, automated synthesis platforms, and machine learning-assisted process optimization. Electrochemical approaches provide valuable potential for development of greener, more efficient and potentially scalable technology for next-generation pharmaceutical manufacturing of peptides.

Keywords

Sustainable peptide manufacturing; peptide bond formation; electrochemical deprotection; electrochemical reactor configurations; flow electrochemistry

Introduction

Peptides have emerged as one of the most important classes of therapeutic molecules because of their high target specificity, excellent biological activity, low systemic toxicity, and ability to regulate protein-protein interactions that are often difficult to regulate using conventional small-molecule drugs. These unique properties make them highly useful in modern medicine, including the treatment of cancer, metabolic disorders, infectious diseases, autoimmune diseases, and cardiovascular diseases. Moreover, peptides play a pivotal role in precision medicine, with applications in molecular diagnostics, vaccine development, biomarker discovery, and targeted drug delivery systems. As the number of peptide-based pharmaceuticals entering clinical development continues to grow, there is a growing need for efficient, cost-effective, and environmentally friendly peptide manufacturing technologies that can deliver high purity and reproducible peptide sequences. Therefore, the improvement of the synthesis of peptides is an important topic of research for both academic and pharmaceutical fields [1,2].

Merrifield's solid-phase peptide synthesis (SPPS) remains the backbone of peptide production because of its simplicity of operation, automation, and high-purity peptide products. However, even after decades of optimization, traditional peptide synthesis has several inherent disadvantages. Large amounts of protected amino acids, stoichiometric coupling reagents, organic bases and dangerous organic solvents like N,N-dimethylformamide (DMF) and N-methyl-2-pyrrolidone (NMP) are needed for repeated cycles of activation, coupling, washing and deprotection of amino acids. These repetitive synthetic steps, which generate high levels of chemical waste, high process mass intensity (PMI), high energy use and high downstream purification, are the reasons why these processes are not economically viable. Therefore, traditional peptide production methods are still costly, energy-intensive and environmentally unfriendly, and alternative environmentally-friendly synthetic approaches that would minimize the use of reagents while maximizing reaction yields and product purity are highly desirable [1-5].

To overcome these problems, a significant effort has recently been directed towards the development of sustainable peptide synthesis technologies. Various interesting alternatives have been investigated, such as environmentally friendly solvents, temporary protecting group methods, catch-and-release purification methods, microwave-assisted synthesis, continuous-flow processing and DMF-free SPPS platforms. In some applications, these innovations have proven effective at lowering the use of solvents and enhancing the efficiency of the operations. But most of these approaches still involve high waste and costly manufacturing, in the form of stoichiometric activating reagents and numerous protecting-group operations. Thus, the design and development of fundamentally new synthetic approaches that can enhance reaction selectivity and reduce environmental impact is an area of ongoing research [3-5].

As part of the new alternatives, electrochemical synthesis has been a subject of great interest because of its sustainability and versatility as a platform for peptide production. Unlike conventional chemical synthesis methods, electrochemical methods use electrons as traceless, clean redox reagents; thus, substrates can be activated directly at the electrode surface under relatively mild reaction conditions. This strategy minimizes the need for dangerous oxidizing or reducing agents and allows for fine-tuning of the reaction potential, current density, and electron transfer. This electrochemical control allows for highly selective transformations, with fewer by-products produced and better atom economy. As a result, electrochemical approaches are now being explored to form peptide bonds, selectively deprotect peptides, functionalize residues, modify peptides at a late stage and perform other useful synthetic transformations that are challenging to perform efficiently through

traditional chemistry. These features make electrochemistry an appealing green alternative for the future production of peptides [6-10]. Significant advances in electrochemical peptide synthesis using a number of novel reaction platforms have been made in recent years. Phosphine-mediated anodic activation has shown great potential for efficient electrochemical peptide bond formation in the absence of traditional coupling reagents, and electron rich phosphine systems have also further extended the scope of the activation to include sterically hindered amino acids and complex peptide sequences. Similarly, anodic amide coupling based on the use of iodide and residue-selective electrochemical functionalization have expanded the scope of electrochemical peptide chemistry by providing highly controlled oxidative transformations. Significantly, these studies have shown that the efficiency of the reaction can be influenced not only by the structure of the substrate but also by electrochemical parameters like the nature of the electrode, supporting electrolyte, solvent composition, applied potential, current density, type of mediator, and the type of cell used. Thus, electrochemical peptide synthesis should be considered not only as an environmentally friendly synthetic method, but as a mechanistically adjustable synthetic platform, which could provide higher reaction selectivity and process flexibility [8-10].

In addition to the progress in reaction chemistry, significant progress has been made in electrochemical reactor engineering. Mass transfer, the utilization of the electrodes, the current efficiency and the residence-time control, to mention only a few, have been significantly improved in modern reactor designs, such as the continuous-flow electrochemical systems, the microreactors, the spinning-electrode reactors, and the parallel-plate flow reactors, among others. The engineering advancements offer valuable opportunities for continuous pharmaceutical manufacturing, including increased productivity, better reproducibility, less overoxidation, and industrial translation. However, several scientific and technological issues remain that hinder a more general application, such as the still narrow spectrum of suitable substrates, the lack of understanding of the mechanism, the fouling of the electrodes, the exclusion of oxidation-sensitive amino acid residues, the lack of standardized electrochemical reporting parameters, and the lack of large-scale validation of the method for the synthesis of peptides in particular [10-12].

Several recent reviews have addressed some parts of electrochemical peptide chemistry, but most focus on a particular reaction methodology or an individual electrochemical transformation. A thorough overview of the state of the art in the critical integration of electrochemical peptide bond formation, peptide deprotection, reactor engineering, sustainability metrics, process scalability, mechanistic understanding, and future manufacturing opportunities is still missing. Moreover, systematic comparison of electrochemical operating parameters and reactor technologies and critical evaluation of existing challenges have been relatively little discussed. These knowledge gaps are crucial to overcome to speed up the translation of electrochemical peptide synthesis from lab-scale demonstration to practical pharmaceutical manufacturing [8-12].

This review provides an extensive, critical overview of recent advances in electrochemical peptide synthesis, with a special focus on electrochemical peptide bond formation, electrochemical deprotection strategies, residue-selective peptide modifications, and new electrochemical reactor technology. The focus is on reaction mechanisms, electrode materials, electrochemical operating conditions, reactor design, sustainability, scalability and some unanswered technical issues that are important for industrial implementation. Finally, the future perspectives on continuous-flow electrochemistry, automated peptide synthesis, green solvent systems, advanced reactor engineering, and machine-learning-assisted process optimization are discussed to provide insights

into the potential directions for the future development of next-generation sustainable peptide manufacturing technologies.

Fundamentals of electrochemical peptide synthesis

The success of electrochemical peptide synthesis is not so much a function of the general concept of “using electrons as reagents” as of the process of how the electrical input is converted into selective chemical activation at the electrode-solution interface. This is of crucial importance in peptide chemistry, as amino acids, protected amino acids, peptide intermediates, and side-chain residues contain multiple redox-active or oxidation-sensitive sites. Thus, the success of an electrochemical peptide reaction is determined not only by the redox event but also by the collective control of the following factors: electrode material, applied current or potential, supporting electrolyte, solvent window, mediator structure, cell geometry and mass-transfer conditions [13-15].

More recent investigations on electrochemical reactions of peptides indicate that selectivity is highly dependent on the substrate. Mild conditions can lead to oxidation or radical-mediated residue-specific modifications of residues such as cysteine, tyrosine, tryptophan, histidine and methionine, which can be problematic during peptide bond formation if uncontrolled oxidation of side chains competes with the activation of the carboxyl. Cysteine is especially sensitive as the thiol side chain is also involved in single-electron transfer and radical addition, in atom-transfer and disulfide-forming pathways, and often needs careful potential control, and transformations of cysteine-containing peptides are often best achieved using mediators or catalysts [14]. This means that yield is not the only factor by which electrochemical peptide synthesis can be evaluated. Other parameters of performance are chemo-selectivity, residue tolerance, site selectivity and peptide integrity. An electrochemical peptide reaction can be either a direct electrolysis in which the peptide substrate or the activating reagent is oxidized or reduced at the electrode or an indirect reaction in which a mediator is first produced electrochemically and subsequently reacts with the peptide substrate in solution. Direct anodic oxidation has been employed for C-terminal peptide modification by decarboxylation of peptide carboxylic acids to give rise to reactive N,O-acetal intermediates which can be trapped by nucleophiles to give C-terminal arylated, sulfonylated or aldehyde functionalized peptides [15, 16]. When direct oxidation of the peptide would also result in side reactions, the selectivity can be increased by using mediated electrolysis. For instance, electrochemical reactivity of a peptide sequence was programmed by incorporating an oxidizable handle during SPPS, allowing tuneable side-chain modification and even peptide stapling through electroauxiliary-assisted oxidation of glutamine-containing peptides [17].

The electrolyte and solvent should be treated as mechanistic variables rather than details. The use of a nitromethane-lithium perchlorate electrolyte system has been demonstrated in the oxidative skeletal modification of proline residues and artificial peptides, which revealed that choice of solvent and electrolyte can stabilize cationic or radical intermediates and provide insight into product pathways [18]. In a similar fashion, solvent control has recently been used for the selective electrochemical decarboxylative acetoxylation of Fmoc-protected peptides for the synthesis of antibody-drug conjugates (ADCs) linkers. The Fmoc group is susceptible to oxidative degradation under traditional Hofer-Moest-type conditions, but under the new conditions of solvent selection, relevant peptides were obtained in 64 to 92 % yield [19]. This example is particularly significant because it directly demonstrates the kind of technical optimization that is necessary for peptide electrosynthesis: the stability of protecting groups, the limit of solvent oxidation, the conversion of substrates and the yield of products must be optimized in tandem.

The nature of the electrode also directly affects the peptide reactions that are obtained. The overpotential, adsorption characteristics, fouling tendency and oxidative/reductive suitability are different for carbon-based electrodes, platinum, boron-doped diamond, glassy carbon, and stainless-steel-type electrodes. The fouling of the electrodes is not a minor operational problem in peptide systems, as peptides and partially oxidized residues will adsorb on the electrode surface, resulting in decreased current efficiency and poor reproducibility. New guidelines in electro-synthesis therefore consider the specification of electrode area, distance between the electrodes, current density, amount of charge passed, electrolyte concentration, type of cell used and the stirring or flow conditions, all of which influence whether or not a reaction is repeatable and reproducible or merely an experimental anecdote [20-22]. Current, current density, electrodes, solvent, electrolyte, cell volume and charge passed are required if a reaction is only described as “constant current electrolysis in an undivided cell” for review.

Another factor that affects reaction performance is the cell design. In an undivided cell the operational simplicity is desirable when the counter-electrode reactions do not interfere with the target transformation. In peptide synthesis, however, the counter reaction may affect pH, create active species or lead to the degradation of labile residues. However, it has now become clear that the counter-electrode reactions play a large part in the electro-organic selectivity, since for each oxidation reaction, a reduction reaction must be occurring and products formed at the counter electrode may be involved in undesirable reactions [21]. These issues can be alleviated by divided cells, but they are accompanied by increased resistance, membrane constraints and scale-up complications. Thus, the selection of divided and undivided cells should be based on sensitivity of the substrate, compatibility of the mediator and behaviour of the counter-electrode and not only on convenience alone.

Controlled-residence electrochemical systems and flow electrochemical systems are more technically interesting for peptide electrosynthesis, as they reduce the distance between electrodes, improve mass transfer, increase the surface area-to-volume ratio of both electrodes, and minimize overoxidation by quickly removing the product from the reaction zone. All these benefits are especially relevant to peptide intermediates, which are sensitive to prolonged exposure to oxidising potential. There are also flow electrochemistry-specific challenges, such as the clogging of poorly soluble peptide substrates, adsorption of substrates on electrode surfaces, the limits of pressure, and the optimization of flow rate, residence time, electrode gap and conversion per pass [22-24]. While organic electrosynthesis has been scaled up from milligrams to grams or even kilograms per day in spinning-electrode and cascade-type electrochemical reactors, similar systematic scale-up studies have not been performed for the formation of the peptide bond and the deprotection of peptides [23,25].

In general, the basics of electrochemical peptide synthesis (Figure 1) need to be comprehended as an integrated reaction-engineering problem. Current literature indicates several promising reactivity aspects such as residue-specific modification, C-terminal functionalization, electro-auxiliary-assisted side-chain modification and protecting-group-compatible decarboxylation. However, many challenges remain, including a lack of standardization in reporting electrochemical parameters, comparative studies of electrodes, optimization of reactors for specific peptides, and quantitative sustainability measures. In future studies, not only the yield of the product, but the current efficiency, the faradaic efficiency, the scope of the substrate, the purity of the peptides, the stability of the electrode, the mass balance and the consumption of charge, as well as the possibility of scaling up, should be reported [26,27]. All these details are crucial and without them,

electrochemical peptide synthesis will remain mechanically interesting but hard to compare, repeat and apply to pharmaceutical peptide manufacturing (Figure 1).

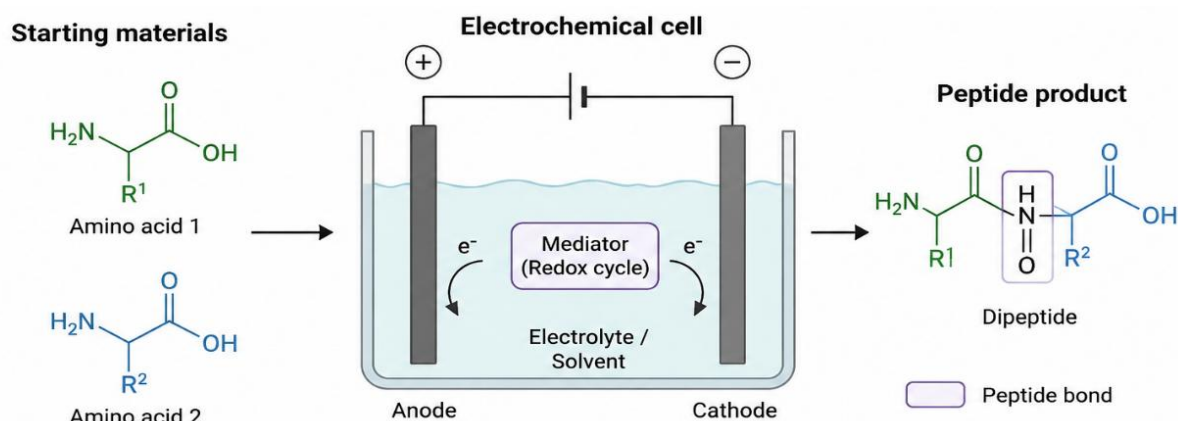


Figure 1. Schematic representation of electrochemical peptide synthesis

Electrochemical peptide bond formation

Reaction logic and performance criteria

Electrochemical peptide bond formation is emerging as an alternative to the traditional methods of peptide bond formation using carbodiimides, uroniums, phosphoniums, and phosphines, which require fewer reagents. Its worth, however, is not just the formation of an amide bond. The main parameters are conversion, isolated yield, controlling racemization, compatibility with protected and unprotected amino acids, regime (existing or potential), electrode pair, solvent/electrolyte system, cell type, charge passed and scalability. This is important because electrochemical activation can also create useful acylating intermediates, but if activation is not well controlled, overoxidation, side-chain oxidation, fouling of the electrodes and reactions promoted by the counter-electrode can occur [28-31].

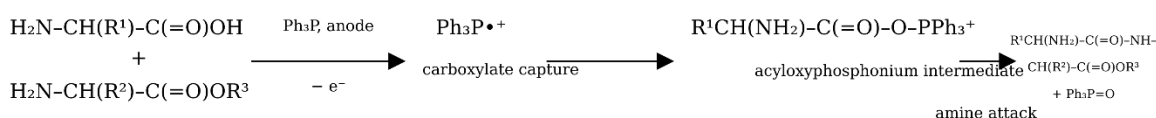
The most relevant development in this field is the application of the electrochemically activated phosphine systems. The principle of the biphasic electrochemical peptide synthesis has been to use the anodic oxidation of triphenylphosphine to form the phosphine radical cation for the activation of the carboxyl group of amino acids for peptide bond formation, with triphenylphosphine oxide (PPh₃O) being the principal stoichiometric by-product[28]. The advantage of this approach is that unlike many traditional coupling-reagent residues, PPh₃O has the potential to be recycled to triphenylphosphine (Ph₃P). The reported method was applicable to the canonical amino acids and it was expanded to the synthesis of the peptide active pharmaceutical ingredient (API) leuprorelin, demonstrating that electrochemical coupling is not restricted to simple model dipeptides [28]. However, even the original system was not a universal approach for sterically hindered amino acids and the results suggested that the efficiency of the electrochemical coupling is not only determined by the oxidation potential of the phosphine but also by the reactivity of the resulting phosphine radical cation.

Phosphine-mediated electrochemical coupling

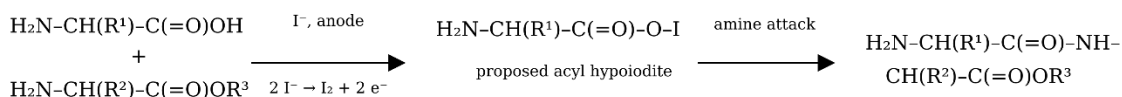
This platform was later enhanced with the use of electron-rich triaryl phosphines in lieu of triphenylphosphine. Electron-rich phosphines were shown to enhance the carboxylic acid activation step and allow extension of the scope to include sterically hindered and useful amino acids, such as difficult oligopeptides, not possible with the previous Ph₃P system [29]. This is important as it demonstrates that electrochemical peptide synthesis is not just a green variant of classical coupling;

it is actually a redox process that can be tuned by varying the substituent effects on the phosphine that directly influence the stability of the radical cation, its activation efficiency and peptide yield. Hence, future studies should report not only yield but also oxidation potential, electrode material, current density, electrolyte, electrolyte-to-solvent ratio, reaction time, and the efficiency of PPh₃O recovery. Other phosphine systems that are mechanistically related but not electrochemical are also of interest as benchmarks. The peptide bonds were formed with a PPh₃-I₂ mediated peptide coupling protocol in 30 min, under open-air conditions, in 64 to 92 % yield with no detectable racemization of coded, non-coded and sterically hindered amino acids [30]. While this is not an electrochemical process, it's useful as a comparator: for electrochemical phosphine systems to be practical, they need to be as fast, as stereoselective, and as substrate-tolerant as these reactions (Figure 2).

A. Ph₃P-mediated electrochemical peptide bond formation



B. Iodide-mediated electrochemical peptide bond formation



R¹ and R² = amino-acid side chains; R³ = protecting group or peptide residue.

Figure 2. Proposed mechanisms of electrochemical peptide bond formation through (A) triphenylphosphine (Ph₃P)-mediated anodic activation and (B) iodide-mediated oxidative coupling

Use of iodide for anodic amide coupling

Another significant model for electrochemical peptide bond formation is the iodide-mediated anodic amide coupling. In this approach, carboxylic acids and amines are joined via an anodic coupling reaction with the aid of iodide mediation and a boron-doped diamond (BDD) anode along with a platinum cathode are reported to be the most efficient combination [31]. This electrode combination is technically relevant because BDD is characterized by a large anodic potential window and can be used for high-potential oxidative processes with reduced degradation of the electrodes. Peptide applications, however, need to be used with caution since BDD-driven oxidation can yield highly reactive radical species which might be able to oxidize sensitive residues like cysteine, methionine, tyrosine or tryptophan. Thus, when using iodide-mediated anodic coupling with peptide substrates, the purity, side-chain tolerance and mass recovery should be considered, in addition to yield. The drawback of many reported electrochemical amide couplings is that quantitative electrochemical data are not fully reported. The following data should be pulled from each article or supporting information and compared for review quality: current density, applied voltage or potential, charge passed, electrolyte concentration; electrode surface area, cell volume, reaction time; isolated yield; and faradaic efficiency. An articulation like “electrochemical coupling was successful” is descriptive and not up to the technical standard requested for a critical review without these values.

Substrate scope, protected amino acids and side reactions

A big question remains as to whether electrochemical peptide bond formation can cope with the complexity of real peptide synthesis. Protected amino acids create difficulties with redox-sensitive groups, and unprotected amino acids with solubility, chemoselectivity and zwitterionic reactivity. Recent direct peptide-bond approaches, other than electrochemistry, indicate the high standards set by other methods. In particular, tris(2,2,2-trifluoroethoxy)silane allowed formation of peptide bonds between unprotected amino acids and amino acid tert-butyl esters in good yields, enantioselectivity and with a wide range of side-chain acceptor amino acids [32]. Likewise, peptide bond formation between unprotected amino acids has been reported using silacyclic dipeptide intermediates to enable convergent synthesis of oligopeptides without the use of the protecting-group strategy [33]. Although these investigations are not electrochemical, their results indicate the demands for the next generation of electrochemical coupling: good chemo-selectivity even in the presence of free amine and carboxyl groups, little epimerization, and acceptable compatibility with polar substrates. The electrochemical peptide modification studies also reveal potential side reactions that are relevant to peptide bond formation. The anodic decarboxylation of peptide carboxylates is an electrochemical C-end modification pathway that results in the formation of N,O-acetal intermediates, which may be trapped with nucleophiles [34,35]. This chemistry is useful but, in the context of peptide coupling, it also alerts to the possibility of terminal carboxylates undergoing decarboxylation rather than potentially productive acyl activation under undesirable potentials. Solvent electrochemical windows have recently been employed to preserve oxidation-sensitive Fmoc groups and selectively transform them with electrochemical decarboxylative acetoxylation of Fmoc-protected peptides (64 to 92 % yields) [36]. The significance of this discovery for peptide coupling is that particular solvents can either cause a protected amino acid to survive the electrolysis or break it down. A comparison of some electrochemical peptide bond formation strategies and their performance metrics is summarized in Tables 1 and 2.

Table 1. Technical comparison of representative electrochemical peptide bond formation strategies and their performance metrics (NR = not reported)

Reaction strategy	Representative substrate(s)	Product/outcome	Mediator/reagent	Electrodes	Solvent/electrolyte	Current/potential/current density	Ref.
Biphasic electrochemical peptide synthesis	Protected amino acids; leuporelin fragments	Dipeptides and oligopeptides	Ph ₃ P radical cation	Carbon anode/Pt cathode	Biphasic organic-aqueous electrolyte	Constant-current electrolysis; current density NR	[28]
Electron-rich triaryl phosphine-mediated electrochemical synthesis	Sterically hindered amino acids and oligopeptides	Peptide bond formation with improved coupling efficiency	Electron-rich triaryl phosphines	Carbon/Pt	Organic electrolyte	Constant-current electrolysis; current density NR	[29]
Iodide-mediated anodic amide coupling	Carboxylic acids and amines	Amide bond formation	Iodide mediator	BDD anode/Pt cathode	Iodide-containing electrolyte	Constant-current electrolysis	[31]
Electrochemical C-terminal peptide modification	Model peptides	N,O-acetal intermediates & peptide derivatives	Anodic decarboxylation	Carbon electrodes	LiClO ₄ /MeNO ₂	Constant-current electrolysis	[34,35]
Solvent-enabled electrochemical decarboxylative activation	Fmoc-protected peptides	Selective peptide functionalization	Anodic decarboxylation	Carbon electrodes	Solvent-dependent electrolyte	Controlled-potential electrolysis	[36]
Industrial-scale electroorganic C–N coupling benchmark	Small organic substrates	C–N bond formation	Electrocatalytic process	BDD electrodes	Industrial electrolyzer	120 mA cm ⁻² , 264 A	[37]
Mn-catalysed electrochemical modification of dehydroalanine peptides	Dehydroalanine containing peptides	Site-selective peptide modification	Mn catalyst	Carbon electrodes	Mn catalyst/electrolyte	Constant-current electrolysis	[38]

Table 2. Technical comparison of representative electrochemical peptide bond formation strategies and their performance metrics (NR = not reported)

Cell configuration	Reaction time, h	Yield, %	Selectivity/purity, %	Faradaic efficiency, %	Scale demonstrated	Major advantages	Key limitations	Ref.
Undivided cell	2 to 6	52 to 89	Good purity; low racemization	NR	API-level peptide synthesis	Avoids stoichiometric coupling reagents; peptide API synthesis demonstrated	Limited substrate scope and incomplete electrochemical metrics	[28]
Undivided cell	1 to 5	61 to 95	High purity	NR	Laboratory scale	Improved coupling efficiency and broader substrate compatibility	Reactor-scale and faradaic efficiency (FE) data not reported (NR)	[29]
Undivided cell	2 to 24	45 to 92	High chemoselectivity	NR	Millimole scale	Mild oxidative activation and broad amide synthesis applicability	Peptide substrate compatibility not extensively investigated	[31]
Undivided cell	1 to 8	40 to 85	Good selectivity	NR	Small scale	Enables late-stage peptide diversification	Not suitable as a general peptide coupling methodology	[34,35]
Batch reactor	2– to 8	64 to 92	High Fmoc integrity	NR	Laboratory scale	Compatible with protected peptides and sensitive functionalities	Limited substrate diversity	[36]
Flow electrolyte	Continuous operation	Process dependent	High conversion	33.5	1 kg in 9 h; 2.6 kg day ⁻¹ throughput	Demonstrates industrial feasibility of electro-organic synthesis	Not peptide-specific	[37]
Undivided cell	2 to 12	55 to 93	Excellent site selectivity	NR	Laboratory scale	Highly selective peptide functionalization	Applicable only to Dha-containing substrates	[38]

Requirements for reactors and scaling up

A disadvantage of many of the reported electrochemical amide couplings is that quantitative electrochemical data are not always reported. Electrochemical peptide bond formation is no longer in the proof-of-concept stage but remains a developing manufacturing platform. Phosphine-mediated anodic activation, anodic amide coupling with iodide and peptide-compatible electrochemical functionalization are the most supported. The key areas are the lack of reporting of current density, charge passed, Faraday's efficiency, electrode area, cell volume, electrode distance, and scaling. In the future, research efforts need to be integrated with both reaction chemistry and electrochemical engineering because, otherwise, the field will stay promising but hard to reproduce, compare and industrialize.

Critical bottlenecks and prospects for electrochemical peptide coupling

One problem with the existing literature is that electrochemical peptide bond formation is still largely viewed as a reaction discovery problem and less a process development problem. In the case of practical electrosynthesis guidance, the influence of current density, electrode area, charge passed, electrolyte concentration, cell geometry and the constant-current or constant-potential control is directly related to the conversion, selectivity and reproducibility [39,40]. Nevertheless, other work in the field of peptides still reports only the electrode pair and the yield of the reaction, leaving out the electrode surface area, the electrode gap, the current density, the faradaic efficiency and the cell volume. This hinders the ability to compare across studies and to assess if a reported coupling is reproducible in another laboratory.

Another underdiscussed aspect is the electrochemical environment associated with peptide synthesis, where anodic oxidation plays a central role in generating the reactive species required for peptide bond formation [41]. This is particularly important in the case of peptides containing the amino acids cystine, methionine, tryptophan and tyrosine, in which competing oxidation can compromise even if the targeted coupling product is achieved. The residue-selective electrochemical modification of peptides and proteins is possible, as has been demonstrated in recent

studies; however, it is also established that peptide side chains are not electrochemically silent functional groups [38,42-46]. Hence, substrate-scope tables containing the following information must be added to future peptide-bond formation studies: redox-sensitive residues, crude purity, isolated yield, level of racemization, and side product profiling.

The biggest translation gap still is reactor design. In flow electrochemistry, the mass transfer is improved, the interelectrode gap is narrow, the residence time is controlled and there is reduced over-oxidation, but solubility, viscosity, adsorption and clogging are issues with peptide substrates [47-49]. Such problems are seldom expressed in a quantitative manner in peptide electrosynthesis. There is also no standardization in the choice of electrode. The overpotentials, adsorption behaviour, fouling resistance and compatibility with radical or ionic intermediates of carbon, platinum, stainless steel, glassy carbon, and boron-doped diamond electrodes differ from one another [50,51]. Low yield without comparative screening of electrodes can be due to poor chemical reactivity or to passivation of the electrodes.

Electrochemical peptide synthesis remains immature, despite recent reviews suggesting promise compared with SPPS and solution-phase peptide synthesis [52-54]. More evidence is needed for sustainability claims. Although conventional and semi-green peptide synthesis platforms have reported greener solvents, reduced solvent burden, improved peptide-manufacturing metrics, and equivalent metrics for waste-composition and energy input are rarely reported for electrochemical peptide coupling. This is an important oversight since “using electrons” does not necessarily mean a “greener” process if a large amount of electrolyte is used, purification is difficult, conversion is low, or current efficiency is low.

However, electrochemical peptide synthesis must transition from proof-of-concept dipeptide couplings to processes with standardized, scalable and quality-controlled workflows for it to be adopted on an industrial scale. Large-scale studies of organic synthesis reveal that only the combination of reaction chemistry with engineering controls, safety, productivity and control of impurities is successful [55]. Hence, future investigations of electrochemical peptide-bond formation should report the following: current density, cell voltage, charge passed, faradaic efficiency, electrode area, cell volume, electrode gap, electrolyte loading, reaction time, yield, purity, racemization, product mass, productivity and recyclability of mediators. The field will be attractive but not fully exploited for pharmaceutical peptide manufacture without these data.

Electrochemical deprotection strategies

Electrochemical deprotection in peptide synthesis has not yet been developed to the same extent as electrochemical peptide bond formation, but it is very relevant, since traditional deprotection still relies heavily on piperidine for the removal of the fluorenylmethoxycarbonyl (Fmoc) group and trifluoroacetic acid (TFA) for the removal of side-chain protection and the cleavage from the resin. These reagents are effective, but they cause safety, regulatory, environmental and side-reaction issues such as aspartimide formation, diketopiperazine formation, electrophile incompatibility, oxidation-sensitive residue damage and acid-promoted modification of tryptophan (Trp), methionine (Met), cysteine (Cys) and tyrosine (Tyr). Hence, in recent years the focus has been on developing orthogonal and milder deprotection strategies that are compatible with the synthetic process.

One good example is the reconsideration of the nitro group as a protecting group for the arginine side chain. The protection of NO₂ proved to be effective in suppressing δ -lactam formation during the incorporation of arginine (Arg) and the NO₂ protection could be removed on resin under mild acidic conditions using SnCl₂ in 2-MeTHF at 55 °C and sonochemistry further accelerated the removal

of NO₂ in several Arg-containing peptides [56]. The advantage of this work is that it deals with a particular side reaction and not with deprotection in general. But the process is chemically reductive, not electrochemical, and involves the use of tin salts. This provides an electrochemical perspective and an opportunity: cathodic or mediated reductive deprotection might be an alternative to metal reductants if selectivity towards Arg-protected peptides can be shown.

The deprotection of Fmoc has also been rethought for sensitive peptides. However, under mildly acidic conditions, [57] reported hydrogenolysis-based Fmoc removal for Z-Arg-Lys-AOMK, a peptide bearing a reactive acyloxymethyl ketone electrophile. This is significant since the classical piperidine-mediated Fmoc removal is not applicable for peptides containing electrophiles. The drawback of the study is that it is not a general solution to sustainable SPPS deprotection, but rather it demonstrates the applicability of orthogonal Fmoc removal in the presence of base-sensitive functional groups. Mild alternatives to catalytic hydrogenolysis such as electrochemical hydrogenation or paired electroreductive systems might be explored.

Brønsted acid and Lewis acid combinations (*e.g.* HCl/FeCl₃ and AcOH/FeCl₃) devised by Pawlas *et al.* [58] are PFAS-free alternatives to TFA, which can be used for final deprotection and peptide-resin cleavage in Fmoc/t-Bu SPPS. A significant quantitative finding is the high degree of iron removal (over 99.99) after cleavage by HCl/FeCl₃. This is important to pharmaceutical translation as the control of any residual metal is an important quality requirement. But there are still areas in need of further investigation, including peptide scope and side reactions that may occur on individual residues, and compatibility with oxidation-sensitive residues. We believe that this is very relevant for future electrochemical deprotection, as Fe(III)/Fe(II) redox cycling could be linked to a controlled electrochemical system.

Another feasible direction would be base replacement for Fmoc removal. Scala *et al.* [59] studied green bases and found DBN to be an efficient base as an effective alternative to piperidine for the rapid removal of Fmoc at low concentrations in green solvents with minimized racemization, particularly in anisole/NOP (75:25). Similarly, Mthethwa *et al.* [60] developed an in situ Fmoc removal strategy that did not require washing after coupling and saved up to 60 % solvent, and that successfully synthesized angiotensin II and afamelanotide with high purity. Although these reports do not involve electrochemistry, they do set up process metrics which electrochemistry must meet less solvent, fewer washing steps, less side reactions and API level peptide compatibility.

The light/photoredox-induced protecting groups also offer valuable insights for electrochemical deprotection. Sun *et al.* reported Picoc-SPPS, a method that involved use of a hydrophilic N α -Picoc group that could be removed under visible-light photocatalysis without using TFA and piperidine, suppressing aspartimide/diketopiperazine formation, and using water and γ -valerolactone as greener media [61]. This is not electrochemical but the study shows that redox triggered protecting groups can enhance selectivity and sustainability. One could imagine electrochemical analogues of Picoc-type protecting groups that would act in response to predetermined potentials, rather than light.

The removal of allyloxycarbonyl (alloc) groups has also become more environmentally friendly. Recently, on-resin removal of alloc was reported using iodine/water in PolarClean/ethyl acetate, followed by one-pot racemization-free peptide coupling, and the process was scaled up to 10 g, in conjunction with TFA-free cleavage, on a 39-aa peptide resin [62]. The deprotection study is one of the most process-relevant ones in considering metal avoidance, long peptide compatibility, one-pot operation, and scale. The difference is that the chemistry mediated by iodine can still be a concern for oxidation sensitive residues; it may be worthwhile to investigate electrochemical generation of iodine under controlled potential.

Lastly, sustainable cyclic peptide synthesis has been combined, aqueous Fmoc/t-Bu SPPS, disulfide formation and TFA/PFAS-free cleavage for atosiban synthesis [63]. As part of a wider body of research on sustainable SPPS and alternatives to Fmoc deprotection [64,65] these works demonstrate that deprotection is no longer a trivial step but a key factor in the purity, sustainability and scalability of peptides. Potential/current, electrode material, electrolyte, solvent, reaction time, conversion, yield, and purity of the peptides, residues, and metal residues/mediators should be reported in future studies if electrochemical deprotection is to become competitive. There are not sufficient electrochemical deprotection case studies in the field at present, which presents an opportunity for future research. The comparison of electrochemical reactor configurations used is represented in Table 3, and a schematic comparison of four electrochemical reactor designs used in peptide and electro organic synthesis is described in (Figure 3).

Table 3. Technical comparison of electrochemical reactor configurations used in peptide and electroorganic synthesis (NR= not reported)

Reactor type	Cell design	Material of construction	Electrodes	Electrode area, cm ²	Electrode gap, mm	Working volume/capacity	Flow rate, mL min ⁻¹	Residence time	Current density, mA cm ⁻²	Productivity/scale	Typical application	Refs.
Divided batch cell	Anode/cathode separated by membrane	Glass/PTFE/Nafion	Carbon, Pt, BDD	1 to 20	2 to 20	10 to 500 mL	NR	NR	1 to 100	mg to g	Sensitive oxidative and reductive peptide transformations	[20,41, 49]
Undivided batch cell	Single compartment	Glass/PTFE	Carbon, Pt, graphite, BDD	1 to 20	2 to 20	5 to 250 mL	NR	NR	1 to 100	mg to g	Peptide coupling, amino acid modification, proof-of-concept electrosynthesis	[28,29,31, 34,35]
Constant-potential flow electrolyzer	Continuous-flow electrolyzer	Industrial electrochemical module	BDD and metal electrodes	Up to 2200	Narrow-gap design	Liter scale	Process dependent	min	120	1 kg, 9 h; 2.6 kg day ⁻¹	Industrial electrosynthesis	[37,66]
Parallel-plate flow reactor	Narrow-gap flow-through cell	PTFE, stainless steel	Carbon felt, graphite, Pt, BDD	10 to 500	0.1 to 1	1 to 100 mL	0.05 to 20	s to min	1 to 100	g to kg	Continuous electrosynthesis and pharmaceutical intermediates	[47, 48]
Microfluidic electrochemical reactor	Microchannel reactor	Glass, silicon, polymer	Pt, Au, carbon	0.01 to 5	0.05 to 0.5	μL to mL	0.001 to 1	s	1 to 100	Analytical to g	Rapid reaction screening and mechanistic studies	[47,49]
Spinning-electrode reactor	Rotating electrode cell	Stainless steel/PTFE	Rotating graphite or metal electrode	10 to 1000	Variable	100 mL to L scale	Continuous feed	s to min	Up to industrial range	g to kg	Scale-up of electroorganic synthesis	[48]

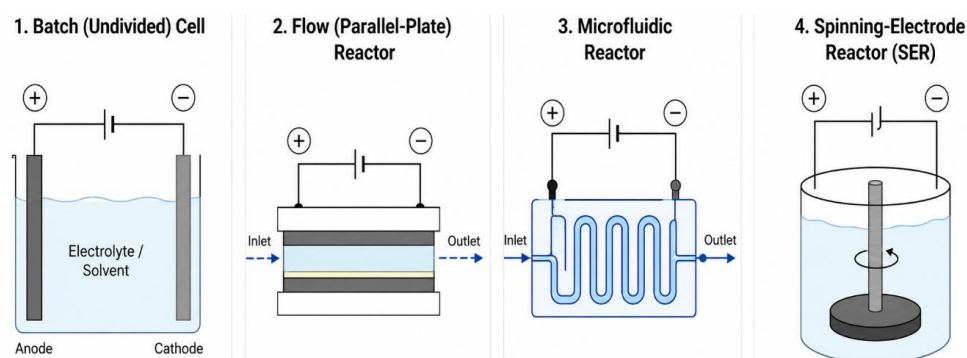


Figure 3. Representative electrochemical reactor configurations employed in peptide and electro organic synthesis, including batch (undivided) cells, parallel-plate flow reactors, microfluidic reactors and spinning-electrode reactors

The electrochemical deprotection should be tested in parallel to the orthogonality of carbobenzoxy (Cbz), Boc and side-chain protecting groups. The cleavage of Cbz is traditionally hydrogenolytic, but an electro reductive cleavage could be performed without the need for pressurized hydrogen and a heterogeneous catalyst, but peptide-compatible potential windows and suppression of competing disulfide or aromatic reduction need to be established.

Cleavage is inherently acid mediated and direct electrochemical removal is less developed; but a realistic electrochemical approach is localized electrogeneration of acid subject to control of acid-sensitive residues, resin linkers and electrode corrosion. Electro responsive groups, like 4,4-dimethoxybenzyloxycarbonyl (Dmoc) and dM-Dmoc, are especially interesting because they can give rise to a fragmentation pathway upon oxidation under externally programmed conditions. The value for the SPPS will be dependent on quantitative evidence of cleavage completeness, by-product capture, resin compatibility, scope of the sequences and true orthogonality to Fmoc/t-Bu and Cbz based protection. This study highlights the potential of electrochemical synthesis for constructing structurally diverse, non-natural peptide derivatives under comparatively sustainable reaction conditions [67-70]. In the future, deprotection studies should be reported on applied potential or applied current density, amount of charge passed, composition of the electrodes, electrolyte, solvent, peptide loading and amount of peptide recovered, yield of the cleavage, and purity of the peptide and the profile of side products. This is a minimum set of data that is important to differentiate a redox trigger of chemical interest from a practically useful deprotection operation [20-22].

Challenges and future perspectives

Although electrochemical peptide synthesis has advanced significantly, several scientific and technological challenges continue to hinder its routine use in pharmaceutical manufacturing. The first key constraint to most reported electrochemical methods is the limited range of substrates they are applicable to. They have been shown to be applicable in most studies with short model peptides or simple amino acid derivatives but are not yet sufficiently explored in the context of complex therapeutic peptides which contain sterically hindered residues, multiple disulfide bonds and/or sensitive post-translational modifications [20,22,33]. In addition, amino acids which are sensitive to oxidation, such as methionine, cysteine, tryptophan and tyrosine, can be prone to unwanted side reactions during electrochemical transformations, which may negatively affect the purity of the products and the yield of the process [18,34].

Another important challenge is that there is not enough knowledge regarding reaction mechanisms. While many studies have been reported where electrochemical coupling and deprotection reactions have been successfully accomplished, the mechanistic pathways, the electron-transfer kinetics and electrode surface phenomena are poorly understood [28,31]. Due to the lack of mechanistic insight, rational process optimization is challenging and prediction of the outcome of reactions with structurally unique peptide substrates is difficult. Furthermore, electrochemical peptide synthesis can involve a variety of different electrode materials, electrolyte solutions, and solvent systems, and the optimal values for the current density and other parameters may differ significantly depending on the specific peptide being synthesized.

There are more difficulties to industrial applications, mainly scalability. While most electrochemical peptide syntheses have been carried out on commercial peptide API which involves leuporelin, need good development to alter these methods toward larger-scale manufacturing with steady product quality [41]. Despite the advantages of continuous-flow electrochemical reactors in enhancing mass transfer, reaction efficiency and scalability, their use in peptide synthesis is still in its infancy [38,49].

This goal of combining electrochemistry with automated solid-phase peptide synthesis (SPPS) platforms and continuous manufacturing systems is still very important and is largely unmet.

However, there are still several electrochemical processes that require toxic solvents or supporting electrolytes or expensive electrode materials, which restricts the environmental and economic benefits [44,58]. Similarly, although some progress has been made in the creation of piperidine-free methods for PFAS cleavage and more environmentally friendly methods for the Fmoc deprotection, it has not been fully implemented to completely remove piperidine and TFA from industrial peptide synthesis [58,60,61]. Hence, it is desirable to focus attention on future research on the development of the whole electrochemical process with green solvents, recyclable mediators and earth abundant electrode material. The other emerging challenge is no one standard reporting practice. Many studies only report a single yield without giving any further information on current efficiency, energy consumption, process mass intensity, electrode stability and impurity profile [24,35]. Such inconsistencies make it difficult to compare between different methodologies and hamper the translation of laboratory findings into industrial processes. It will therefore be important to develop standard metrics for the assessment of electrochemical peptide synthesis in the future. In the future, a few research avenues seem promising. Combining electrochemistry with flow chemistry, photochemistry and reaction optimization using machine learning could result in very efficient and predictable reactions platforms for peptide production [45,48]. Selective deprotection, site-specific peptide modification, late-stage functionalization and macrocyclization of peptides by electrochemical approaches have also not been extensively investigated and have great potential for future research in this area [56-58,60-64]. Moreover, redox responsive protecting groups and electrochemically stimulated orthogonal approaches might provide a completely new paradigm in peptide assembly and purification. The electrochemical peptide synthesis has progressed from a proof-of-concept technique to a potential manufacturing technology. Many disciplines will have to be integrated, however, to make this potential a reality, including synthetic chemistry, electrochemical engineering, computational modelling and process analytical technology. Overcoming the current challenges in selectivity, scalability, sustainability and understanding of the mechanisms will be essential to make electrochemical methodologies viable and commercially valuable technologies for the next generation peptide production (Table 4).

Table 4. Current challenges, knowledge gaps, and future opportunities in electrochemical peptide synthesis

Challenge	Specific problem	Evidence from literature	Impact on peptide synthesis	Current mitigation strategies	Remaining gap	Future opportunity	Ref.
Electrode fouling/passivation	Adsorption of peptides and oxidation products on electrode surfaces	Carbon and metal electrodes suffer from surface deactivation during prolonged electrolysis [20,50]	Reduced conversion and reproducibility	Electrode polishing, flow systems, BDD electrodes	Long-term electrode stability data are lacking	Development of anti-fouling electrode coatings and self-cleaning electrodes	
Limited substrate scope	Most studies use model amino acids and short peptides	Poor translation to therapeutic peptides	Restricts industrial applicability	Testing of protected amino acids and oligopeptides	Lack of studies on long and complex peptides	High-throughput screening and machine-learning-guided substrate prediction	[28,29]
Incomplete mechanistic understanding	Radical and ionic intermediates are poorly characterized	Difficult process optimization	Limits rational reaction design	Mechanistic and computational studies	Few operando electrochemical investigations	<i>In situ</i> spectroscopy and computational electrochemistry	[31,42]
Inadequate reporting standards	Current density, FE, charge passed, and reactor dimensions are often omitted	Poor reproducibility and comparison between studies	Hinders technology development	Review recommendations and reporting guidelines	No standardized framework exists	Establishment of reporting guidelines for peptide electrosynthesis	[39,40]

Challenge	Specific problem	Evidence from literature	Impact on peptide synthesis	Current mitigation strategies	Remaining gap	Future opportunity	Ref.
Scale-up limitations	Most reactions remain at milligram scale	Industrial translation is difficult	Low productivity	Flow electrochemistry and spinning-electrode reactors	Lack of peptide-specific reactor studies	Continuous manufacturing and modular flow reactors	[48,66]
Electrolyte and solvent compatibility	Electrolytes may affect peptide stability and purification	Increased impurity burden	Additional downstream processing	Green solvents and recyclable electrolytes	Limited systematic studies	Development of peptide-compatible electrolyte systems	[36,58]
Deprotection challenges	TFA and piperidine remain dominant	Environmental and safety concerns	High process mass intensity	PFAS-free cleavage and greener bases	Few electrochemical deprotection strategies	Redox-responsive and electrochemically cleavable protecting groups	[58, 60-62]
Reactor engineering limitations	Limited training data, operation, design and scale-up of electrochemical cells	Difficult process optimization	Restricts scale-up and technology transfer	Adoption of electroorganic reactor designs	Lack of peptide-specific engineering studies	Digital twins and AI-assisted reactor optimization	[47]

Emerging trends and future perspectives

The electrochemical peptide synthesis as a manufacturing reality requires parallel development of scalable reactor technologies, intelligent automation, and seamless integration with the pharmaceutical production pipeline. While the previous sections have highlighted the amazing advances in bond formation and protecting-group manipulation as well as side-chain modification that have been made possible by electrochemistry, these advances will only be realized to their full industrial potential when the corresponding reactor platforms become mature enough to meet the requirements of regulated, large-volume peptide production.

The most significant hardware development in this arena is continuous-flow electrochemical reactors. In contrast to batch cells, flow reactors provide a well-defined electrode–solution interface, greatly enhance mass and charge transport, and provide rigorous control of residence time, all of which are important for the reactive intermediates that are typically found in peptide electrochemistry. Basic engineering concepts for the transfer of batch electroorganic reaction to continuous-flow reaction have been reviewed thoroughly, such as residence-time distribution, electrode stack design, 3D-printed cell fabrication and electrochemical cell coupling to downstream workup modules [71]. Complementary high-throughput continuous flow methods also show how parallelised screening, automated fraction collection and in-line analytics can reduce the reaction discovery to optimised conditions cycle time by orders of magnitude [72].

Miniaturised electrochemical microreactors have been the first step towards the fast screening of reaction conditions with minimal amounts of materials, particularly valuable Fmoc-amino acid building blocks and peptide intermediates [73]. At the other extreme of the demonstration size range, for instance, the electrochemical oxidation of thioethers [42]. Selectivity has been demonstrated even with large-area electrodes. Closed-loop, self-optimizing platforms are now quickly replacing traditional one-factor-at-a-time optimization in electrochemical synthesis. Today, automated slug-based electrochemical flow platforms are available that combine design-of-experiment (DoE) algorithms with programmable potentiostats and in-line spectroscopic analysis to find the best current density, mediator loading and solvent composition in hours, instead of weeks [74]. Going one step further, electrochemical systems have been designed that can self-optimize for densely functionalised targets, and then the result of the experiment drives the decisions for the next conditions, without a human involved [75]. Real-time nuclear magnetic resonance spectroscopy (NMR) and Fourier-transform infrared spectroscopy (FTIR) process analytics can be used to demonstrate multi-objective autonomous platforms that aim for maximisation of yield, minimisation of solvent waste and constraint of processing time for multi-

step API sequences. The same principles can be easily adapted to telescoped peptide electrochemistry workflows, where the successive steps of peptide coupling, deprotection and peptide modification are all necessary to be carried out without the need for human intervention. The engineering paradigm that the field is transitioning towards is the "tech-enhanced synthesis" paradigm, which is the general idea of a unified digital architecture that includes continuous flow hardware, electrochemical reactors, and data-driven tools [76,77].

Along with a strong hardware platform, validated digital control strategies and modular connectivity will be needed to bridge the gap between research-scale electrochemical reactors and good manufacturing practice (GMP) compliant pharmaceutical manufacturing. As an example of electrochemical modules being used as individual unit operations in a fully automated API production train, automated remote optimisation of multistep, multiphase continuous-flow processes for pharmaceutical synthesis using a combination of Bayesian optimisation with programmable pump networks and inline sensors is demonstrated [78]. Now continuous-flow reactions have been used at various stages of the pharmaceutical development of APIs and fine chemicals and electrochemical steps are increasingly regarded as intrinsically cleaner than the use of stoichiometric oxidants or reductants in otherwise traditional sequences [79]. Perhaps the most visionary integration is the development of a fully programmable, modular chemputation platform for automated peptide synthesis. Such systems involve synthetic instructions that are encoded as machine-readable protocols that are carried out on plug-and-play hardware modules, and that could form the basis for the architectural design of incorporating electrochemical coupling, deprotection and modification steps directly into automated peptide assembly workflows [80]. The simultaneous standardisation of reactor interfaces and open-source control software should reduce the implementation hurdles of using electrochemical modules in current solid-phase peptide synthesis (SPPS) automation systems.

Scalable peptide electrochemistry is heading towards a combination of modular flow reactor design, closed-loop AI-driven optimisation and automated pharmaceutical process integration. Some of the challenges yet to be addressed include the development of electrode materials that can be used for an extended period of time under continuous peptide synthesis conditions, in-line analytical methods that are robust enough to track complex peptide intermediates and regulatory frameworks that can accept non-conventional electrochemical unit operations in drug substance manufacturing processes. These obstacles are being gradually overcome and electrochemical methods are poised to provide sustainable, efficient, and scalable processes for the synthesis of peptide therapeutics at industrially relevant scales.

The most likely general platform for controlled peptide oxidation or mediated coupling is the narrow-gap parallel-plate flow cell, which has a high electrode area-to-volume ratio, low ohmic loss and short residence times. The advantages of microreactors are their high throughput in terms of rapid screening and mechanistic mapping, but there are also disadvantages, such as low single-channel throughput and clogging. Spinning-electrode systems offer good mass transfer and are not limited by boundary layers but involve moving parts, seals and are subject to scale-dependent hydrodynamics, which make validation difficult. Cells with divided electrodes shield sensitive peptide intermediates from the counter-electrode products, but add resistance and fouling to the system along with extra cleaning steps [38,45,46,71-74]. A manufacturing-ready system should thus be made up of the following features: modular numbering-up, replaceable or clean-in-place electrodes, in-line temperature and pressure monitoring, controlled residence-time distribution and process analytical technology for conversion and impurity tracking. Constant-potential control is

beneficial when a small selectivity window is desired, but constant-current is easier to operate and is often more rugged when scaling up. For peptide-specific demonstrations, space-time yield, faradaic efficiency, energy consumption, electrode lifetime, solvent/electrolyte recycling, batch-to-batch reproducibility, and downstream purification burden should be reported. The best scale-up evidence currently exists for non-peptide electroorganic processes, but there is still a valid opportunity to translate peptide electrosynthesis into industry [24,37,42,72-75].

Conclusion

Electrochemical peptide synthesis is a novel, green technique that uses electrochemically controlled redox processes as an alternative to reagent-based activation methods and has proven promising for peptide synthesis. Recent developments in electrochemical peptide bond formation, selective deprotection, residue-specific peptide functionalization and electrochemical reactor engineering have shown the promise of such methods to increase the efficiency, chemoselectivity, and sustainability of reactions, and to drastically decrease the amount of chemical waste and hazardous chemicals used. In addition, new opportunities for the translation of laboratory electro-synthetic methodologies to industrial peptide production are now emerging with the development of continuous-flow electrochemical systems, microreactors, and scalable reactor technologies. However, the latter is still relatively immature in terms of technology. There are still some key issues to be resolved before industrial use can be realised. These include the extension of the substrate scope to include structurally complex therapeutic peptides, better understanding of the mechanism of electrochemical activation pathways, reducing electrode fouling and passivation, greater reproducibility of reactions, standardisation of reporting and the development of scalable reactor systems for peptides. To overcome these challenges, synthetic chemists, electrochemical engineers, pharmaceutical scientists, and process analytical specialists will need to work closely together. Future research efforts should be directed towards combining electrochemical synthesis with continuous manufacturing systems, automated peptide synthesis, modular flow reactors, artificial intelligence optimization of processes, and sustainable solvent systems to further enhance the efficiency of peptide manufacturing and its environmental footprint. Furthermore, the creation of recyclable mediators, earth-abundant electrode materials, electrochemically responsive protecting groups and advanced reactor designs will further enhance the utility of electrochemical methods.

In summary, electrochemical peptide synthesis is a rapidly developing and revolutionary area of green chemistry, reaction engineering, and pharmaceutical production. Reaction design, reactor technology, and process optimization will continue to evolve, and electrochemical methodologies will emerge as a practical, scalable, and environmentally responsible platform for peptide-based pharmaceutical production in the near future.

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