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## Focus on therapeutic peptides and their delivery

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### ABSTRACT

Peptides are bioactive intermediates between small organic molecules and large biological compounds like antibodies or proteins. These compounds play a unique and valuable role as therapeutic agents, owing to their unique biochemical properties and versatility in treating a wide range of diseases such as metabolic disorders, cancer therapy, antimicrobial and anti-inflammatory agents. The global peptide therapeutics market is projected to exceed USD 50 billion by 2024, reflecting the increasing demand and interest in this field. Therapeutic peptides offer an optimal balance of specificity, safety, and molecular size, providing greater precision in targeting specific receptors with fewer off-target effects and reduced toxicity compared to small-organic drugs. Peptides also exhibit enhanced tissue penetration and present simpler, cheaper manufacturing processes with lower immunogenicity. To date, around 100 peptides have attained clinical approval in major markets, with nearly half of these approvals occurring in the past 20 years. This trend highlights the growing importance and therapeutic potential of peptides in modern medicine, explaining the substantial market associated with these treatments. The review presents a detailed comparison of the major parenteral administration modes for therapeutic peptides, specifically subcutaneous and intravenous routes. We highlight how these methods impact the pharmacokinetic profiles of peptides and influence patient outcomes, providing critical insights into the advantages and limitations of each route. Finally, a significant aspect of this review is its focus on innovative drug delivery systems and formulations designed to address the challenges of peptide delivery, namely stability, bioavailability, and therapeutic efficacy.

### 1. Introduction

Peptides, short chains of amino acids, serve as targeting molecules often categorized between small organic molecule and large biological compounds (e.g. antibodies, growth factors...). Their targeting properties make them valuable for both diagnostic and therapeutic with wide range of biomedical applications (e.g. Leuprolide for cancer therapy, Semaglutide for diabete, Dalbavancin as an antimicrobial agents, Voclosporin as an anti-inflammatory agents...) (Lau and Dunn, 2018). Their unique characteristics as therapeutics arise from an optimal balance between specificity, safety, and bioavailability. Compared to small-organic drugs, therapeutic peptides offer greater precision in targeting specific cell receptors, resulting in fewer off-target effects and reduced toxicity. Unlike other biologics, therapeutic peptides are generally smaller, facilitating enhanced tissue penetration. Peptides present

simpler and cheaper manufacturing processes, along with lower immunogenicity. Collectively, these attributes render therapeutic peptides versatile and efficient in modulating biological processes (Lau and Dunn, 2018).

To date, around 100 peptides have attained clinical approval in major markets, including the United States, Europe, and Japan. Almost half of these approvals have occurred within the past 20 years. Additionally, more than 450 peptides are currently in preclinical and clinical evaluation (Muttenthaler et al., 2021) underscoring the growing interest and potential of such therapeutics. The market value and patient reach of peptide-based therapeutics have been on a consistent rise globally. In 2017, the global sales of these therapeutic peptide drugs amounted to USD 20 billion. Projections indicate that by 2025, sales will exceed USD 50 billion, with an annual growth rate (CAGR) of 9.0 % over the period from 2025 to 2033 (Lau and Dunn, 2018; Center for Drug Evaluation

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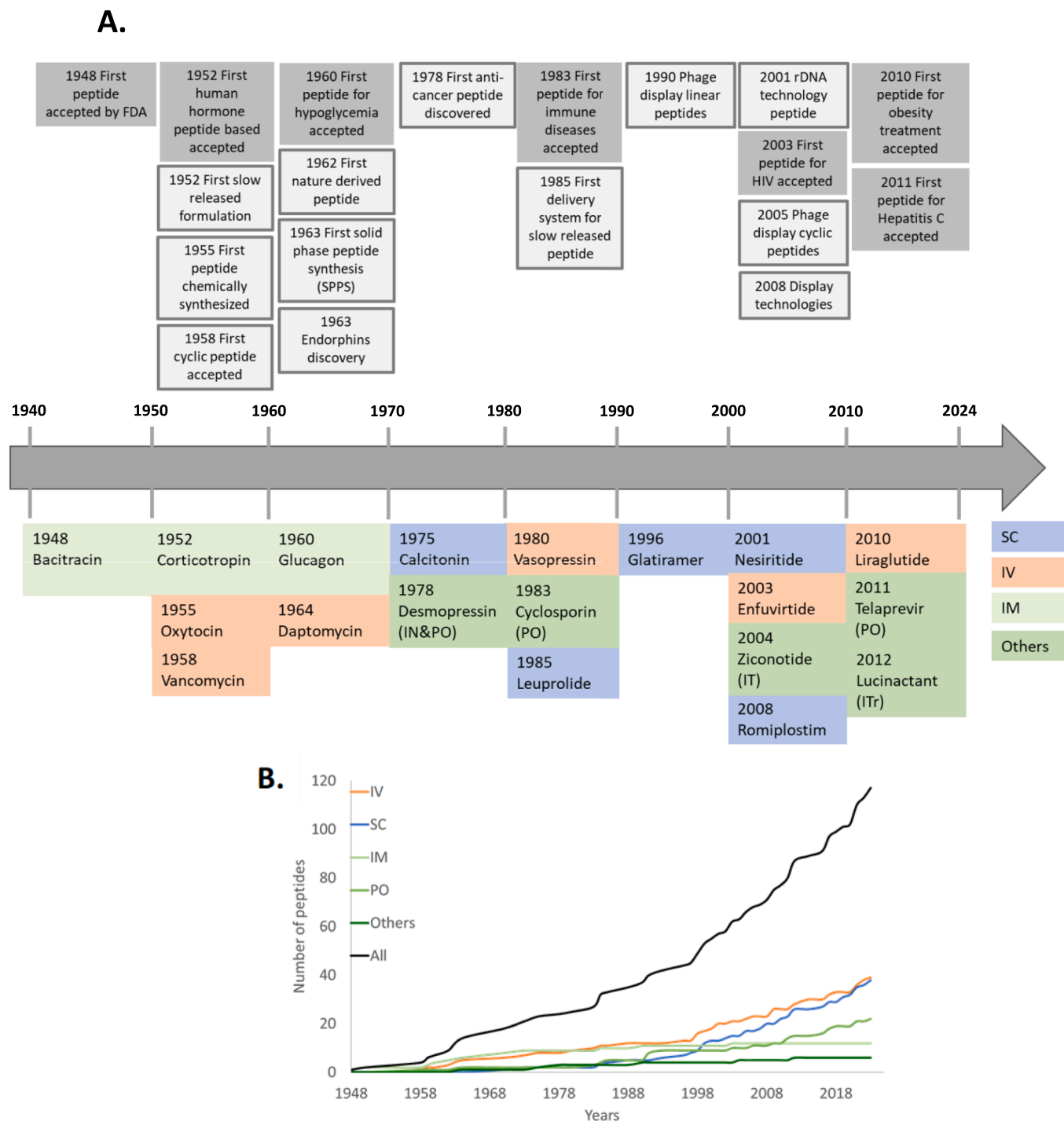
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and Research, « Novel Drug Approvals for, 2023 ; Jørgensen, 2015; Insights, 2025).

This review will begin by exploring the growing interest in therapeutic peptides, highlighting key milestones in their development—from the approval of the first U.S. Food and Drug Administration (FDA)-regulated peptide to the present. The review will

examine technological advancements as well as the expanding fields of application for these peptides. This review will then offer a comprehensive overview of peptides currently in clinical use and those under clinical investigation, emphasizing the diverse applications of this versatile class of therapeutics. Administration routes of therapeutic peptides will be presented, with a focus on intravenous and subcutaneous



**Fig. 1.** Technological evolution of peptides through decades (A) Timeline in peptide acceptance by FDA. Top: key milestones in scientific developments. Bottom: Key example of FDA-approved peptides and their routes of administration. IV: intravenous administration, SC: subcutaneous administration, IM: intramuscular administration, PO: per os administration, IN: intranasal administration, IT: intrathecal administration, ITr: intratracheal administration (B) Number of peptide-based drugs approved by the FDA in the timespan of 1950–2023. Each peptide is counted by its route of administration. Peptides administered through multiple routes are counted multiple times if necessary, and according to the year of FDA approval. References (Lau and Dunn, 2018; Muttenthaler et al., 2021; Center for Drug Evaluation and Research, « Novel Drug Approvals for, 2023 ); (Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024; Sharma et al., 2023 ); (Fetse et al., 2023) and FDA TIDES approvals were used for this Figure.

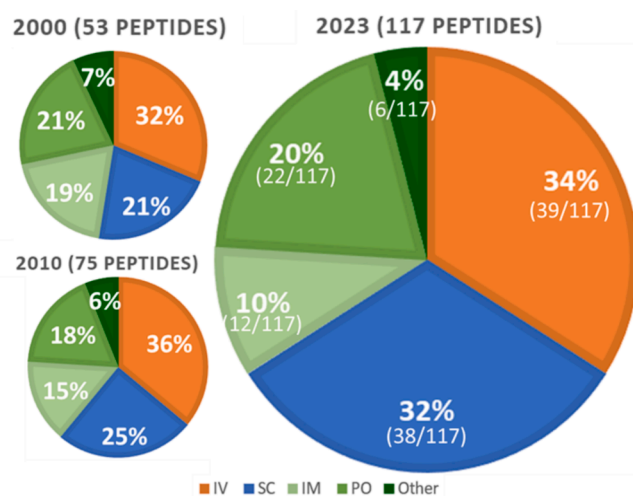
delivery, which continue to be the most commonly used methods of administration. Finally, the review will address the challenges faced by therapeutic peptides and explore formulation strategies and innovative delivery systems designed to overcome these limitations in order to enhance the therapeutic potential of these biomolecules (Lau and Dunn, 2018; Muttenthaler et al., 2021; Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020).

For the purpose of this review, peptides will be defined as oligopeptides consisting of 2 to 50 amino acids, following the classification proposed by Lau and Dunn (Lau and Dunn, 2018) and Zhang et al. (Zhang et al., Sep. 2020). This definition distinguishes peptides from larger protein molecules, such as Insulin. The focus here will be on therapeutic peptides that have received approval from the FDA. All data and information have been updated as of December 2024 (Center for Drug Evaluation and Research, « Novel Drug Approvals for, 2023 ; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024); (Sharma et al., 2023) . For Figs. 1, 2, 3, and 5, references (Lau and Dunn, 2018; Muttenthaler et al., 2021; Center for Drug Evaluation and Research, « Novel Drug Approvals for, 2023 ); (Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024; Sharma et al., 2023) ; (Fetse et al., 2023) were used, along with the annual FDA TIDES approvals, providing a comprehensive overview of all therapeutic peptides currently on the market. When the same formulations are manufactured by different companies or provided in different doses, such formulations are counted only once in this review. We exclude epitope-specific vaccine peptides, diagnostic-only peptides, peptide linkers, and have made the choice to limit our focus on therapeutic peptides. Indeed, epitope-specific vaccines are designed to trigger an immune response rather than provide direct therapeutic effects. Diagnostic peptides are used for disease detection and monitoring, not treatment. Peptide linkers serve as connectors in biotechnological applications and lack therapeutic properties.

## 2. Growing interest and development of therapeutic peptides

### 2.1. Advantages of therapeutic peptides over traditional small molecules and other biologics

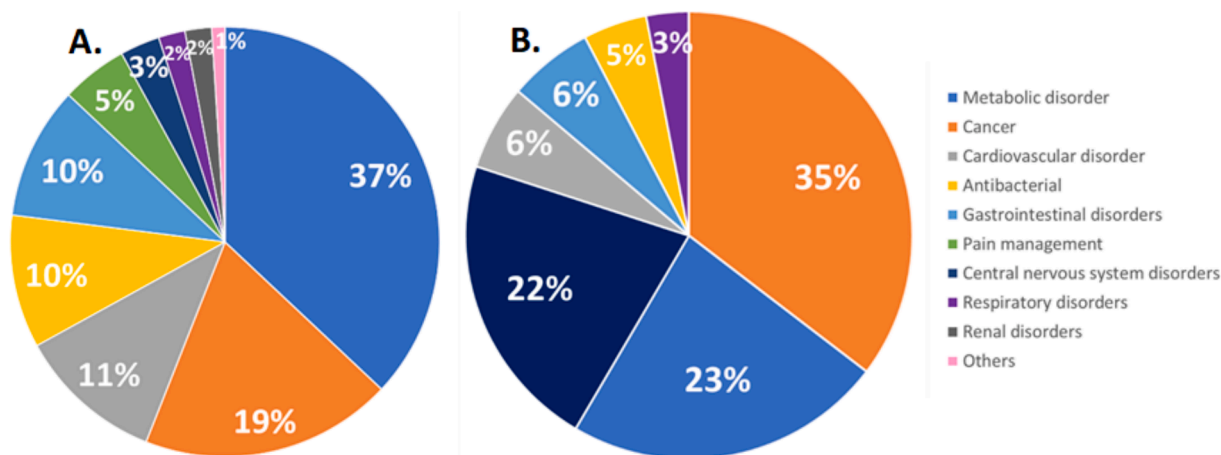
Therapeutic peptides offer distinct advantages over small molecules, antibodies and proteins (Sharma et al., 2023; Vlieghe et al., 2010; Fetse et al., 2023) making them highly competitive for a wide range of therapeutic and diagnostic applications (Wang et al., 2022; Craik and Kan,



**Fig. 3.** Distribution of peptide drug routes over time. A peptide administered through multiple routes is taken into account for each routes of administration. However, different doses of the same peptide within the same route is counted only once. References (Lau and Dunn, 2018; Muttenthaler et al., 2021; Center for Drug Evaluation and Research, 2023) ; (Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024; Sharma et al., 2023) ; (Fetse et al., 2023) and FDA TIDES approvals were used for this Figure.

2021).

Compared to small molecules, peptides offer superior selectivity and specific binding affinity toward therapeutic targets (Rossino et al., 2023). This leads to higher therapeutic efficacy as well as reduced systemic toxicity and fewer off-target side effects (Rossino et al., 2023; Zou et al., 2024). However, the plasma half-life of peptides is typically very short (e.g., of the order of minutes for some unmodified peptides, see Table S1) to some extent, due to the action of several peptidases that degrade them. This vulnerability comes from their relatively simple structure, which includes easily accessible peptide bonds that these enzymes specifically target for cleavage (Shi and Di, 2022). Furthermore, peptides also exhibit rapid renal and hepatic clearance in the human body (Fosgerau and Hoffmann, 2015). This is a disadvantage compared to small molecules, which generally exhibit greater *in vivo* stability. Additionally, peptide manufacturing is often more complex



**Fig. 2.** Distribution of FDA-Accepted Therapeutic Peptides and Peptide-Based Drugs by Pathology (2024) (A) Distribution of the FDA-accepted therapeutic peptides according to the different pathologies. The total number of FDA-approved peptides in 2024 is 101. (B) Distribution of Pathologies Treated with Peptide-Based Drugs Approved in Clinical Trials According to Table S2. A peptide used for different indications in different clinical trials is counted multiple times. Criteria of drug selection for this includes active clinical trials which are not recruiting currently. The total number in 2024 is 66. References (Lau and Dunn, 2018; Muttenthaler et al., 2021; Center for Drug Evaluation and Research, « Novel Drug Approvals for, 2023 ); (Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024; Sharma et al., 2023) ; (Fetse et al., 2023) and FDA TIDES approvals were used for this Figure.

and labor-intensive compared to small molecules. This complexity arises from the need for precise synthesis steps, which often involve multiple coupling and deprotection stages. Moreover, the purification process for peptides can be challenging, requiring extensive optimization of techniques such as high-performance liquid chromatography (HPLC) to achieve the desired purity. In contrast, small molecules usually involve fewer synthesis steps and are easier to purify and stabilize, making their manufacturing process more straightforward (Al Musaimi and Jaradat, 2024).

Compared to larger molecules, such as proteins and antibodies, peptides are smaller and more flexible. Unlike proteins and antibodies which possess complex and stable secondary and tertiary structures, peptides typically exhibit linear structures or simple loops, contributing to their flexibility. This flexibility allows peptides to target both extracellular and intracellular receptors with high specificity. However, unlike proteins, which have folded structures that shield part of the chains from potential degradation, peptides are fully solvent-exposed. This makes them more vulnerable to oxidation, hydrolysis, and deamidation. While antibodies are highly specific and effective in targeting extracellular proteins or circulating antigens, their large size restricts tissue penetration and renders them ineffective against intracellular targets. Peptides, on the other hand, are small enough to penetrate tissues and cross cell membranes, enabling them to access intracellular proteins, enzymes, and signaling pathways that are typically beyond the reach of antibodies (Vlieghe et al., 2010; Craik et al., 2013; Hummel et al., 2006; Ghosh et al., 2018). In contrast to proteins and antibodies, which often elicit stronger immune responses and have longer half-lives, therapeutic peptides can be designed to minimize immunogenicity, offering a safer profile for patients (Holz et al., 2023). However, the short *in vivo* half-life of peptides compared to the longer half-life of proteins, can pose challenges, as it may impact their efficacy within biological systems. From a production perspective, peptides are easier and less expensive to manufacture than proteins and antibodies (Craik et al., 2013).

Nonetheless, peptides represent a middle ground between the ease of production and relatively low cost of small molecules and the highly specific but costly and complex nature of antibodies (Trier and Houen, 2023). In summary, while small molecules offer stability and ease of administration, and larger molecules provide unmatched specificity for extracellular targets, therapeutic peptides hold a unique role in drug development.

## 2.2. Short story of peptides development

The therapeutic peptides market has experienced remarkable growth over the past decades, driven by significant scientific advancements in their design and production (Fig. 1) (Craik et al., 2013). The Fig. 1A presents a timeline illustrating scientific developments, with key milestones highlighted at the top and the major FDA-approved peptides listed in the lower part.

### 2.2.1. First discoveries

Therapeutic peptide story began in the mid-twentieth century with the first peptide accepted by the FDA, Bacitracin, in the 1940 s. This peptide is an antibiotic peptide produced by bacterial strains to treat bacterial skin infections after intramuscular administration (Aronson, 2016; Awais et al., 2007). The 1950 s marked a pivotal era, with the introduction of peptides derived from human hormones, notably Corticotropin, which stimulates the adrenal glands to produce cortisol, aiding in the management of stress and inflammation. During this period, researchers also gained deeper insights into the relationship between peptide structure and activity, leading to the synthesis of the first artificial peptide, Oxytocin, in the 1950 s. This peptide is used to induce labor, manage postpartum hemorrhage, and support breastfeeding (Vigneaud et al., 1953). Oxytocin was both the first synthetic peptide and the first peptide to be administered intravenously. This breakthrough marked the beginning of modern peptide-based therapies.

### 2.2.2. Peptide synthesis innovations

The 1960 s, marked a turning point in peptide synthesis with the invention of solid-phase peptide synthesis, commonly known as Merrifield synthesis. Developed by Robert Merrifield (Merrifield, 1963), this technique revolutionized peptide chemistry by enabling the sequential and automated production of peptides with high precision. This breakthrough greatly facilitated the creation of custom-designed peptides, transforming both peptide research and manufacturing. Currently, 85 % of therapeutic peptides are chemically synthesized by the Merrifield process (Zhang et al., Sep. 2020).

The 1980 s brought further advancements, including optimized solid-phase synthesis, improved coupling reagents, advanced purification methods, and automated production. These technological leaps enabled the synthesis of complex peptides with enhanced pharmacological activity, stability, and therapeutic potential, consolidating peptides' growing roles in biotechnology and medicine.

Another major advancement in peptide synthesis came in the 1990 s with the introduction of linear phage display, a technique using bacteriophages to display peptides or proteins on their surface. This innovation enabled rapid identification of peptides with high affinity for specific targets, accelerating drug discovery for cancer, autoimmune, and neurodegenerative diseases. Linear phage display remains an important tool in drug development and continues to be an invaluable asset in drug discovery today (Lau and Dunn, 2018; Muttenthaler et al., 2021; Smith and Petrenko, 1997; Sidhu, 2000; Bratković, 2010).

In the 2000 s, the synthesis of therapeutic peptides advanced significantly with the introduction of recombinant DNA (rDNA) technology, cyclic phage display, and other display technologies. rDNA technology involves combining DNA from different sources to produce peptides and proteins with high precision and efficiency. Cyclic phage display is a technique used to create and screen large libraries of cyclic peptides, which are displayed on the surface of bacteriophages, to identify those with high affinity for a target protein or molecule. Cyclic peptides, which their circular structure, are often identified using these display technologies, which enhance their stability, binding properties and resistance to degradation (De Clercq, 2009; Vora et al., 2022). These advancements have greatly expanded the potential for developing new peptide-based therapeutics (Wu et al., 2016).

### 2.2.3. Emergence of new indications for peptides

The development of therapeutic peptides has been shaped not only by advancements in synthesis techniques but also by the discovery of new indications. In the 1960 s, critical discoveries in peptide biology, such as identifying endorphins and brain-produced opioid peptides (Hughes et al., 1975; Li and Chung, 1975) reshaped the understanding of peptides' role in physiological processes. In 1962, the discovery of Calcitonin, the first animal-derived peptide, further highlighted the therapeutic potential of peptides, particularly in the treatment of endocrine and hormonal disorders (Copp et al., 1962). The following decade saw the discovery of the first anti-cancer peptide, Leuprolide, for prostate cancer treatment, marking a significant milestone in medical research. This breakthrough laid the foundation for the development of peptide-based oncology treatments, offering new hope for targeted cancer therapies.

In the 1960 s, the first studies on metabolic disorders were initiated with the introduction of Glucagon in 1960. However, it was not until the 2010 s that the peptide therapeutics market truly flourished with new approvals for conditions such as obesity and type 2 diabetes. One notable example is Liraglutide, a GLP-1 receptor agonist for diabetes and weight management. Another key development was the approval of Leuprolide, the first commercial anti-cancer peptide, a peptide analog of luteinizing hormone-releasing hormone (LHRH) for advanced prostate cancer (Wex et al., 2013; O'Brien and Hibberd, 1990). This breakthrough in peptide therapy enabled more convenient treatment schedules and improved patient compliance. Meanwhile, interferons, such as interleukin and gamma interferon, cytokine peptides with antiviral,

antiproliferative, and immunomodulatory properties, were introduced for conditions like certain cancers, viral hepatitis, and autoimmune diseases (Sharma et al., 2023; Billiau and Matthys, 2009). The emergence of new indications for therapeutic peptides was also marked by the 2003 approval of the first therapeutic peptide for HIV, Enfuvirtide, a significant advance in HIV treatment. This milestone highlighted the potential of peptides in treating complex diseases and opened new avenues for their application across various therapeutic areas (Vlieghe et al., 2010; Smith and Petrenko, 1997; Bratkovič, 2010; De Clercq, 2009).

#### 2.2.4. Emergence of long-acting peptides and delivery systems

Advancements in therapeutic formulations began as early as the 1950 s, with the approval of Acthar Gel in 1952. Acthar Gel, used to treat conditions such as infantile spasms, multiple sclerosis, lupus, sarcoidosis, and various forms of arthritis, including psoriatic and rheumatoid arthritis. This formulation of Corticotropin, prepared with gelatin and administered intramuscularly or subcutaneously either twice daily or once daily depending on the indication and medical condition, allowed for the prolonged release of Corticotropin (Wan et al., 2023; Madan et al., 2016). Advancements in sustained-release formulations continued in the 1980 s, with the 1985 approval of the first formulation for the slow release of Leuprolide (Lupron Depot). These developments improved delivery efficiency, led to more patient-friendly therapies, and further solidified peptides' role in modern medicine (Lau and Dunn, 2018; Muttenthaler et al., 2021; Zhang et al., Sep. 2020; Vlieghe et al., 2010). The 1990 s, also saw significant advancements in peptide delivery systems, including liposomes, nanoparticles and controlled-release delivery systems, which enhanced the efficacy and safety of treatments (Vora et al., 2022; Liu et al., 2022; Zhang et al., 2022). This topic will be explored in more detail in part 4.

Additionally, in the 90 s' the therapeutic peptide market expanded with the introduction of Somatostatin analogs, offering greater stability and a longer duration of action compared to natural Somatostatin. Analogs such as Octreotide and Lanreotide were designed to have extended half-lives, providing sustained therapeutic effects for conditions like acromegaly and neuroendocrine tumors.

The new millennium opened novel route of administration for therapeutic peptides, highlighted by the approval of the first intrathecal peptide, Ziconotide, in 2004 (Bolognesi and Cavalli, 2016; Miljanich, 2004; Olivera and Teichert, 2007). This breakthrough laid the groundwork for the development of therapeutic peptide opening up new possibilities for the administration.

#### 2.2.5. Peptides: Rising Numbers and market impact

These advancements have positioned therapeutic peptides as key players in the modern pharmaceutical landscape. As shown in Fig. 1B, the number of FDA-approved peptides for various routes of administration has grown steadily over the years. In the 1970 s, only around ten peptide-based drugs were available. By the 2000 s, this number had risen to nearly 50 FDA-approved therapeutic peptides, and today, it is close to 100. From an economic point of view, peptides represent a market value of approximately USD 43.45 billion in 2023 and a projected compound annual growth rate (CAGR) of 6.1 % from 2024 to 2030, highlighting their rising significance in modern medicine ('Peptide Therapeutics Market Size Share Analysis - Growth Trends Forecasts, 2024'; 'Peptide Therapeutics Market Size Share Report, 2024'). This growth is mainly also due to the increasing prevalence of cancer, osteoporosis, obesity and diabetes, which has stimulated demand for peptide-based therapies.

### 3. Current use of therapeutic peptides

#### 3.1. The current landscape of therapeutic peptides

Today, the market for therapeutic peptides spans a wide range of

applications (Lau and Dunn, 2018; Zhang et al., Sep. 2020; Sharma et al., 2023; Fetse et al., 2023), as illustrated on Fig. 2.A and detailed in Supporting Information (Table S1). This dual function of targeting and therapeutic action positions peptides as versatile and promising agents in the development of new therapeutic strategies.

The treatment of metabolic disorders, including diabetes, dominates the global peptide therapeutics industry with an estimated share of over 37 % in 2024, representing approximately 14.9 billion dollars ('Peptide Therapeutics Market Size And Share Report, 2024'). These conditions are becoming increasingly prevalent due to the rise in sedentary lifestyles, unhealthy eating habits, and excessive alcohol consumption. As a result, therapeutic peptides for these pathologies represent a substantial segment of the peptide industries. One example is Liraglutide, a peptide used to treat type 2 diabetes. It is a glucagon-like peptide-1 (GLP-1, receptor agonists), which specifically targets hormone receptors to increase glucose levels. Liraglutide also plays several roles in modulating insulin secretion, reducing hepatic glucose production, enhancing insulin sensitivity, and controlling appetite (DeVries et al., 2012; Pabreja et al., 2014).

The rising prevalence of cancer worldwide, coupled with the growing awareness among healthcare providers and patients about the adverse effects of chemotherapy and radiation therapy, is also driving the development of alternative medicines such as peptide-based drugs. Cancer treatment currently accounts for a significant proportion of peptide therapeutics, representing around 19 % of peptide-based treatments (Muttenthaler et al., 2021). In cancer therapy, peptides are designed to target receptors that are overexpressed on cancer cells (Thundimadathil, 2012). A notable example is Goserelin, a gonadotropin-releasing hormone (GnRH) analogue primarily used for treating prostate and breast cancer by lowering testosterone and estrogen levels (Karami Fath et al., 2022). The key advantage of using peptides in these therapies is their ability to minimize the impact on healthy cells, allowing for targeted action directly on tumor cells. Indeed, peptide can be designed to bind specifically to receptors or molecules that are overexpressed on tumor cells. This selective binding ensures that the therapeutic action is concentrated on the cancer cells, sparing healthy cells.

Cardiovascular diseases, the leading cause of death and morbidity worldwide (Wang et al., 2022), can be treated with therapeutic peptides that specifically target receptors in the cardiovascular system. Cardiovascular diseases account for a significant proportion of peptide therapeutics, ranking third with around 11 % of peptide-based treatments (Muttenthaler et al., 2021). Natriuretic peptides, such as Nesiritide, are used in heart failure treatment by inducing diuresis and vasodilation, effectively reducing the heart's workload. By decreasing blood volume, these peptides minimize the fluid the heart has to pump, while also lowering vascular resistance and pulmonary pressure, leading to improved cardiac function (O'Connor, 2011; Colucci et al., 2000).

Therapeutic peptides modulate immune responses and reduce inflammation in various other pathologies. For example, in gastrointestinal diseases, Teduglutide can inhibit proteases that contribute to chronic Inflammatory Bowel Diseases (IBD) like Crohn's disease and ulcerative colitis (Cochrane, 'Peptide Therapy in Gastrointestinal Disorders', Cochrane Handbook, Jun., 2024; Liddle, 2024). Another example is Glatiramer Acetate which is specifically employed in the treatment of multiple sclerosis, demonstrating the potential of therapeutic peptides to offer targeted and effective management of autoimmune disorders (Larché and Wraith, 2005; Filippi et al., 2001; Khan et al., 2005). Autoimmune diseases are on the rise due to various factors, including environmental and lifestyle changes such as pollution, infections, stress, and dietary modifications, which predominantly affect high-income countries. As a result, the use of peptides in this field of application is expected to continue evolving and expanding in the coming years.

Finally, peptides are effective in managing pain by targeting pain receptors in the nervous system (Janecka et al., 2010). Ziconotide,

derived from cone snail venom, is specifically used to alleviate severe pain in patients who do not respond to opioids (Safavi-Hemami et al., 2019).

Peptides find application in the treatment of diverse conditions, including endometriosis, respiratory disorders, renal and dermatological conditions, as well as in antimicrobial therapies. In summary, as displayed in Fig. 2, the wide-ranging applications of therapeutic peptides highlight their significant potential in addressing various medical conditions.

### 3.2. Clinical research and future directions

The future for therapeutic peptides is remarkably promising, with around 100 peptides currently in clinical trials (active and recruiting clinical trials), including 19 % in phase 3 clinical trials (Fig. S1 and Table S2). Among those peptides, some have already been approved and are now under study for new routes of administrations as is the case of Semaglutide, approved in 2017 for subcutaneous administration for the treatment of type 2 diabetes which is currently in phase 1 clinical trials for oral administration (NCT04109508). Another example is the research of new indication as for Dalbavancin. Initially approved by the FDA in 2014 for treating acute bacterial skin and skin structure infections, this peptide is now being tested for a new indication: treating osteoarticular infections associated with hip and knee prostheses (NCT05046860). While these peptides are designed for already-explored diseases such as metabolic disorders and bacterial infections, exciting technological advancements are also accelerating peptide drug discovery. For example, early-stage clinical trials and preclinical models have shown promise for peptide-addressable targets lacking approved drugs. Examples include kisspeptin analogs for assisted reproduction (NCT01667406) (Abbara et al., 2015) and MC4R agonists for genetic obesity syndromes (NCT02507492) (Kühnen et al., 2016). Innovative therapies, such as amyloid inhibitors, are also being designed to combat beta-amyloid aggregation in Alzheimer's disease (NCT04491006), alongside neuroprotective peptides in pre-clinical research to safeguard neurons in Parkinson's disease (Baig et al., 2018; Fox, 2013). Neurodegenerative diseases are of critical importance in high-income countries due to their significant contribution to disability and healthcare costs, as well as their impact on the aging population, which is more prevalent in these regions.

Fig. 2.B shows that the use of therapeutic peptides is evolving, particularly in terms of the pathologies treated with significant difference between currently accepted peptides and one under clinical trials. Currently, peptides are predominantly in clinical trials for cancer treatment, representing 35 % of all clinical trials. Metabolic disorders remain an important part of clinical trials (23 %), although their proportion has decreased compared to peptides already on the market (37 %). What is particularly remarkable is the rise in treatments for central nervous system pathologies, which now represent 22 % of clinical trials, compared to only 3 % of peptides currently accepted by the FDA.

Advancement in screening methodologies and computational biology, including artificial intelligence, accelerates peptide discovery. Techniques such as metabolomic, proteomic, and genomic screening can identify bioactive peptides with unique structural features (Goles, 2024). A better understanding of human genetic disorders could also lead to new therapeutic peptide candidates; identifying natural ligands for peptide receptors could reveal new receptor-ligand interactions.

New approaches in peptide drug delivery, formulation, and half-life extension are enhancing this class of molecules (Lau and Dunn, 2018). With these advancements, we stand on the verge of delivering more effective, targeted, and safer treatments for some of the most challenging medical conditions.

## 4. Various route of administration

### 4.1. Presentation and temporal evolution

As highlighted in Figs. 1 and 3, different routes have been used for the administration of therapeutic peptides since the 1950 s (Lau and Dunn, 2018; Zhang et al., Sep. 2020; Ganesh et al., 2021). Today, 9 administration routes have been approved. Fig. 3 represent the evolution of approved administration for intravenous (IV), intramuscular (IM), subcutaneous (SC) (Zhang et al., Sep. 2020) and oral (PO) routes (Haddadzadegan et al., 2022; Philippart et al., 2015), as well as other routes including intrathecal (IT) (De Martini et al., 2023), intratracheal (ITr) (Patton, 1999), intranasal (IN) (Patton, 1999), intracavernous (IC), sublingual (SL) and topical (TOP) pathways (Zhang et al., Sep. 2020).

PO administration remains popular with 20 % of peptides approved for oral administration in 2023. This route is highly studied and holds significant interest due to its potential to improve patient compliance (For a comprehensive understanding, readers are directed to recent reviews that thoroughly examine this topic) (Drucker, 2020; Gupta et al., 2013; Gleeson et al., 2021). However, it presents challenges due to peptides' sensitivity to digestive enzymes, degradation caused by drastic changes in pH in the gastrointestinal tract, and limited mucosal permeability, all of which reduce bioavailability (Haddadzadegan et al., 2022; Philippart et al., 2015; Drucker, 2020; Tran and ElSayed, 2021). As a result, parenteral routes continue to be the most frequently used routes for about 80 % of peptide administration. For this reason, the rest of this review will focus on parenteral routes.

Within the parenteral route, administration methods have evolved significantly. For example, in the early 2000 s, IM injections accounted for approximately 20 % of peptide administration but this had since declined to just 10 %. In contrast, SC delivery has gained prominence increasing from 21 to 32 % over the same period. This shift likely reflects the growing focus on enhancing patient comfort, as IM injections often cause discomfort, especially with frequent dosing (Meibohm, 2019). Moreover, SC administration offers the advantage of gradual release for sustained effects (Meibohm, 2019). Notably, intravenous (IV) administration has remained stable over time, consistently accounting for 32–36 % of peptide administrations.

This trend is also evident in research, spanning from preclinical to clinical stages, where the administration trends align closely with those observed in FDA-approved peptides. As shown in Fig. S1 (A), IV and SC routes dominate, together comprising 63 % of all peptide administrations. A notable trend in clinical trials is the sharp decrease in IV (intravenous) administration research, indicating a shift away from this approach. The subcutaneous route, on the other hand, continues to gain interest. Moreover, innovations in less invasive delivery, such as pulmonary administration, are emerging as promising alternatives in clinical trials (Vora et al., 2022).

In summary, both in research and among approved therapies, IV and SC administration are currently the primary mode of delivering therapeutic peptides and will be detailed in the following sections.

### 4.2. Intravenous and subcutaneous: The current predominant route of administration

#### 4.2.1. Formulation

Parenteral formulation as SC and IV must meet specific criteria during development to ensure safety and efficacy and prevent local irritation, discomfort, and hemolysis. This includes being sterile and free of pyrogens, as well as having appropriate pH, injection volume, and tonicity for the chosen route.

The IV route can accommodate significantly larger volumes in comparison with SC, which is essential for treatments like infusions. As a result, SC administration often requires higher peptide concentrations, given the limited injection volumes (~5 mL) (Usach et al., 2019). This poses challenges related to peptide self-association, especially for

amphiphilic peptides. At higher concentrations, these peptides can aggregate through hydrophobic interactions, forming micelles. While these aggregates can enhance chemical stability by reducing solvent exposure, the aggregation can also negatively affect pharmacokinetics, bioavailability, and physical stability. Excessive aggregation may lead to gelation or precipitation, compromising the quality and effectiveness of the formulation. Indeed, when peptides aggregate, they can lose their functional structure, which reduces their biological activity. Aggregates can also form gel networks, making the solution more viscous or even solid.

#### 4.2.2. Pharmacokinetics of peptide after administration

IV administration offers several advantages over the SC route. It led to 100 % bioavailability as it is administered directly into the bloodstream. This is especially important for drugs that require precise and rapid dosing. Therapeutic effects are almost instantaneous due to direct delivery into the circulatory system. Additionally, it provides precise control over dosing. However, there are still significant advantages to SC administration compared to IV administration.

Table 1 and Fig. 4 present pharmacokinetic parameters following SC or IV administration for various peptides used in clinical practice. Several key observations can be highlighted. Generally, IV administration results in a higher maximum concentration ( $C_{max}$ ) compared to SC. For instance, in the case of Sandostatin, the  $C_{max}$  is 9.6  $\mu\text{g/L}$  for IV versus 2.4  $\mu\text{g/L}$  for SC.

The time to reach maximum concentration ( $T_{max}$ ) is also shorter with IV administration, reflecting the direct delivery into the bloodstream, whereas SC administration shows a delayed  $T_{max}$  due to the slower, more gradual absorption. For example, Bleomycin has a half-life of 0.25 h after IV (Fig. 4A) and 4.3 h after SC (Fig. 4B).

The area under the curve (AUC), which represents total drug exposure, can be similar between the two routes, as seen with Sandostatin.

The volume of distribution ( $V_d$ ) is often comparable. Lastly, clearance rates can differ slightly, with SC administration sometimes showing slightly higher values, as with Leuprolin Acetate. These variations are crucial for determining the optimal route of administration based on therapeutic requirements of each drug.

#### 4.2.3. Benefits and drawbacks for patients

Both IV and SC administration routes present advantages and drawbacks for patients, as outlined in Table 2. IV administration offers rapid onset, precise dose control, and easier formulation. However, it comes with several disadvantages, including the need for hospital-based administration by trained personnel, potentially long administration times, pain and discomfort associated with the procedure, risk of infection, persistent ecchymosis, short half-life, and the need for frequent administration.

On the other hand, SC administration is generally more patient-friendly with the potential for self-administration and fewer severe local or systemic reactions, making it an attractive option for chronic conditions like diabetes and hormonal therapies (Overton et al., 2021). However, SC administration has some limitations. It is more immunogenic, allows for only low administration volumes, and carries a risk of hypersensitivity. Additionally, the peptide must cross several biological membranes before reaching systemic circulation, which slows absorption. This prolonged exposure to enzymes and other factors increases the risk of degradation. SC administration is also particularly challenging for peptides with short half-lives, as their rapid degradation can compromise therapeutic efficacy (Mueller and Adler, 2018).

Despite their high potency, proteins and peptides are limited by their short *in vivo* half-life and low bioavailability as discussed in the first part of this review in section 1.1. These limitations often necessitate frequent dosing since short half-lives lead to the rapid elimination of therapeutic peptides. This can negatively impact patient quality of life, reduce

**Table 1**

Main pharmacokinetic parameters of different peptide drugs administered intravenously and subcutaneously. RoA. Route of administration, AUC. Area under the curve. IV administration achieves a higher  $C_{max}$  and faster  $T_{max}$  due to direct bloodstream delivery, while SC administration has a delayed  $T_{max}$  due to slower absorption. Both routes have comparable AUC.

Peptide	RoA	Formulation	$C_{max}$ ( $\mu\text{g.L}^{-1}$ )	Half life (h)	AUC	Volume of distribution	Body clearance	$T_{max}$ (h)	Administration
Sandostatin	IV (Pharma, 1989)	Solution	9.6	0.17 to 1.5	5.6 $\mu\text{g.h.L}^{-1}$	0.27 L/kg	2.7 $\text{mL.h}^{-1}$	sec	50 $\mu\text{g}$ (push of 3 min)
	SC (Chanson et al., 1993)	Solution	2.4	>1.6	5.3 $\mu\text{g.h.L}^{-1}$	0.27 L/kg	2.7 $\text{mL.h}^{-1}$	0.5	50 $\mu\text{g}$
Peginesatide, 2024; ( Czerniak et al., 2014) (Committee for Medicinal Products for Human Use, 2013)	IV	Solution	$2.10^{-3}$	25	3 $\text{ng.h.mL}^{-1}$	34.9 $\text{mL.kg}^{-1}$	0.5 $\text{mL.h}^{-1}.\text{kg}^{-1}$	sec	100 $\mu\text{g.kg}^{-1}$
	SC	Solution	$4.10^{-4}$	53	2 $\text{ng.h.mL}^{-1}$	35.6 $\text{mL.kg}^{-1}$	1.5 $\text{mL.h}^{-1}.\text{kg}^{-1}$	48	100 $\mu\text{g.kg}^{-1}$
Leuprolin acetate ( AbbVie, 1986)	IV	Solution	200	2.9	125.8 $\mu\text{g.h.L}^{-1}$	27 L	8.3 $\text{L.h}^{-1}$	sec	1 mg
	SC SC, 2018; ELIGARD, 2024)	Solution (Okada et al., 1991)	32.3	3.6	118.6 $\mu\text{g.h.L}^{-1}$	37 L	9.1 $\text{L.h}^{-1}$	0.6	1 mg
		Solution depot (Mostafa et al., 2014); (Periti et al., 2012); (Sethi and Sanfilippo, 2009)	47.4	N.A	990.5 $\mu\text{g.h.L}^{-1}$	33.5 L	8.34 $\text{L.h}^{-1}$	24	7.5 mg 1 a month
Liraglutide (Elbrønd et al., 2002); ( Jacobsen et al., 2016)	IV	Solution	70	8	810 $\mu\text{g.h.L}^{-1}$	5 L	1.7 $\mu\text{L.h}^{-1}.\text{kg}$	sec	5 $\mu\text{g.kg}^{-1}$
	SC	Solution	17	15	503 $\mu\text{g.h.L}^{-1}$	11 L	0.6 $\text{L.h}^{-1}$	9.3	5 $\mu\text{g.kg}^{-1}$
Bleomycin ANSM, 2013; (Hall et al., 1982)	IV	Solution	$1-10.10^3$	0.25	7.3 $\text{ng.h.L}^{-1}$	$13 \text{L.m}^{-2}$	1.13 $\text{mL.h}^{-1}.\text{m}^{-2}$	sec	30 mg
	SC	Solution	$0.9.10^3$	4.3	5 $\text{ng.h.L}^{-1}$	$17 \text{L.m}^{-2}$	0.78 $\text{mL.h}^{-1}.\text{m}^{-2}$	1	30 mg

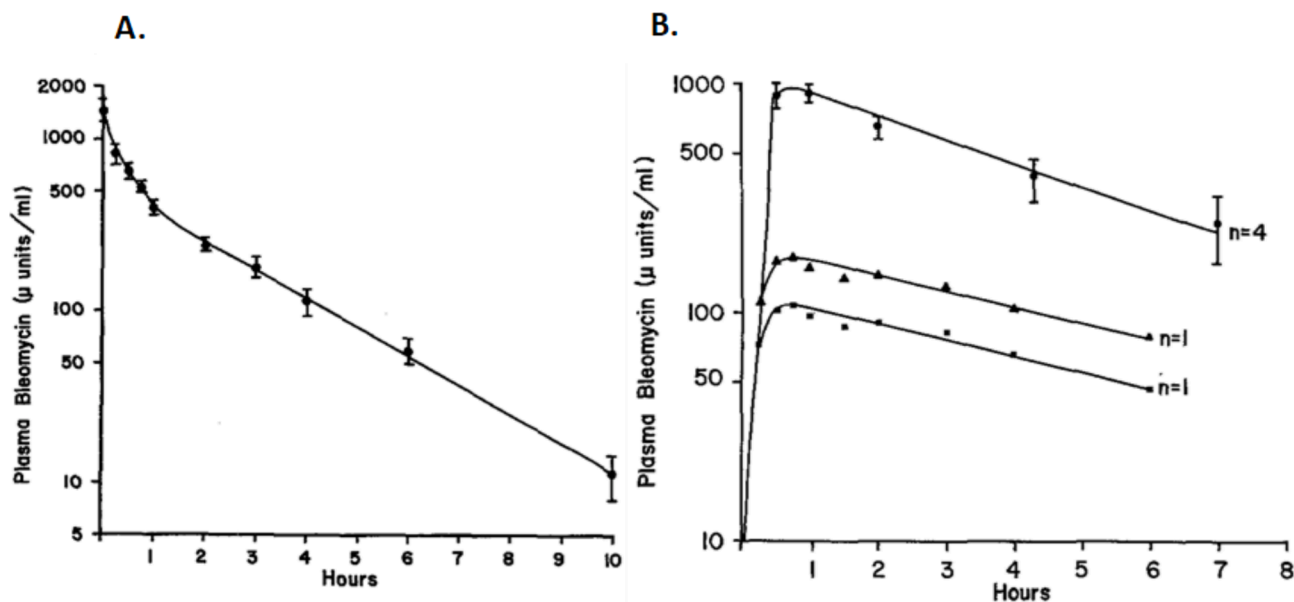


Fig. 4. (A) Mean plasma bleomycin disappearance in six patients who received 15 units of bleomycin IV. (B) Mean plasma bleomycin concentration in four patients who received 30 units SC (●). Bleomycin plasma concentrations on day 1 (■) and day 2 (▲) in one patient who received four units of bleomycin SC every 6 h. Issued from S.W. Hall et al (Hall et al., 1982).

Table 2

Comparisons of Advantages and disadvantages of intravenous administration, subcutaneous administration and subcutaneous administration with an injectable delivery system.

	IV (McLennan et al., 2005); (Renard, 2008); (Lundin et al., 2002); (Viola et al., 2018)	SC (McLennan et al., 2005; Pivot et al., 2014; Frost, 2007; Ballard, 1968)	SC + injectable delivery system (McLennan et al., 2005; Pivot et al., 2014; Frost, 2007; Ballard, 1968)
PROS	No delivery delay Easier to formulate No problem of vascular access	Self-administration possible Short administration time Patient preference Fewer side effects Longer half life Suitable for local and systemic exposure	Reduced dosing frequency Reduces the degradation of active ingredients Controlled and prolonged release Easy administration of hydrophobic compound Improved delivery of poorly soluble compounds
CONS	Hospital administration (need of trained personal) Can be long administration Pain and discomfort associated with administration Risk of infection and persistent ecchymosis Short half life Frequent administration	More immunogenic Low administration volume Potential degradation of active ingredients Hypersensitivity	Biocompatibility of delivery system Biodegradability of delivery system Risk of immunogenic reaction Limited drug payload

compliance, and lead to poor adherence to the treatment regimens. To address these challenges, various strategies have been developed, including chemical modifications of peptides and the use of advanced delivery systems. These approaches aim to enhance solubility, control release, extend dosing intervals, improve bioavailability, and reduce side effects.

## 5. Long-acting peptides and delivery systems

In this section, we limited our study to intravenous, intramuscular, and subcutaneous administration as they remain the main routes of administration of therapeutic peptides.

### 5.1. Formulation and chemical modifications of therapeutic peptides

#### 5.1.1. Formulation

To address the challenges associated with therapeutic peptides, several formulation modifications can be implemented (Fominaya et al., 2015).

Peptides are often susceptible to chemical modification and enzymatic degradation. Stabilizers such as sucrose, trehalose, and myoinositol protect peptides by preventing denaturation and aggregation, thus extending their active lifespan (Patel et al., 2023). Surfactants like polysorbate 80 and sodium lauryl sulfate are used to enhance solubility by reducing surface tension, improving peptide dispersion in aqueous solutions, which facilitates administration and absorption (Balandin et al., 2024). Peptides are also prone to degradation or oxidation by metals, so chelating agents such as EDTA (ethylene diamine tetracetic acid) and citric acid are employed to bind to metal ions, preventing them from damaging the peptides and preserving their integrity (Song et al., 2017). Many therapeutic peptides also suffer from poor aqueous solubility, and excipients such as polyethylene glycol (PEG), mannitol, and cyclodextrins are often incorporated to improve stability and solubility. All these excipients can chemically interact with peptides, potentially altering their structure, stability, and efficacy. Excipients may also influence how peptides cross biological membranes or affect metabolic pathways. Therefore, careful evaluation of peptide-excipient interactions is crucial to ensure the efficacy and safety of the final formulation (Martinez et al., 2022; Panakanti and Narang, 2012).

In addition to improving stability and solubility of peptides, formulation can also be optimized for slower peptide release. For example, Acthar Gel is formulated with 16 % gelatin, a natural substance derived from the partial hydrolysis and denaturation of collagen, to provide a prolonged release after intramuscular or subcutaneous injection. This formulation allows for a slower release of the peptide, which has a rapid half-life of 15 min (Wan et al., 2023; Madan et al., 2016) but Acthar Gel

still have to be administered one to two times a day. Another key example of sustained-release formulation is Somatuline Depot, the first sustained-release formulation produced via peptide self-assembly. Upon injection, Lanreotide forms a depot at the injection site, from which the drug is continuously released into surrounding tissues, likely through passive diffusion, and then absorbed into the bloodstream. After a single administration, Lanreotide is steadily released from the depot with a half-life of 23–30 days, achieving a bioavailability of up to 78.4 % in healthy subjects (Burness et al., 2014). This technique takes advantage of peptide aggregation but is not universally applicable to all peptides and does not address peptide protection from enzymatic degradation.

### 5.1.2. Chemical modifications

Chemical modifications of therapeutic peptides can take various forms (Vlieghe et al., 2010). First modification of the peptide sequence of therapeutic peptides have been shown to offer multiple benefits. Sequence modifications can enhance the stability of peptides, enabling them to better resist enzymatic degradation and extend their duration of action (Fominaya et al., 2015). Additionally, these changes can optimize biological activity by increasing the affinity, specificity, or selectivity for molecular targets. Modifications can also improve pharmacokinetics by altering absorption, distribution, metabolism, and elimination, thereby boosting bioavailability (Adessi and Soto, 2002). Moreover, sequence modifications can help avoid immunogenic epitopes, reducing the likelihood of triggering an immune response. An example of sequence modifications is teriparatide (Forteo). Teriparatide is a recombinant form of parathyroid hormone used to treat osteoporosis. During its development, specific sequence modifications were made by substituting some amino acids to minimize the presence of immunogenic epitopes, which are parts of the peptide. This sequence modification aimed to reduce the likelihood of the body recognizing teriparatide as a foreign substance, thereby decreasing the risk of adverse immune reactions.

Peptide cyclization involves forming a covalent bond between amino acids of the peptides, creating a cyclic structure. This modification offers numerous advantages over linear peptides. Cyclic peptides exhibit enhanced stability due to their compact three-dimensional conformation, making them less vulnerable to enzymatic and chemical degradation (Gentilucci et al., 2010). These cyclic peptides are also more resistant to proteolysis, resulting in prolonged half-life and enhanced efficacy. Additionally, their unique structure improves bioavailability by facilitating easier passage through biological membranes, as they can adopt conformations that favor diffusion across lipid bilayers. Furthermore, the compact nature of cyclic peptides enhances binding affinity and specificity while reducing immunogenicity, making them promising candidates for therapeutic applications (Gentilucci et al., 2010; White and Yudin, 2011; Góngora-Benítez et al., 2014). For instance, Octreotide, used to treat acromegaly and neuroendocrine tumors, is a cyclic analogue of Somatostatin. The cyclization of octreotide enhances its stability and extends its half-life by 30 times, allowing for less frequent administration (Hill et al., 2014; Harris, 1994).

Other chemical modification of peptide by glycosylation, PEGylation (Gentilucci et al., 2010; Goodwin et al., 2012; Acar et al., 2017), acylation (Gentilucci et al., 2010), or lipidation (Gentilucci et al., 2010) have also been studied. These modifications enhance the potential of therapeutic peptides by prolonging half-life, improving stability, reducing immunogenicity and side effects, and increasing solubility. For example, Liraglutide and Exenatide are two PEGylated therapeutic peptides used for the treatment of type 2 diabetes. In Exenatide's case, PEGylation has been specifically explored to extend its half-life and enhance stability, allowing for less frequent dosing (Goodwin et al., 2012). A study demonstrated that a PEG conjugate achieved a remarkable 56-fold extension of Exenatide's half-life in rats (Schellenberger et al., 2009), highlighting the significant impact of such chemical modifications on therapeutic efficacy.

Another effective strategy for enhancing therapeutic peptide is the conjugation with carrier molecules. For example, Albiglutide, a

modified version of Exenatide for treating type 2 diabetes, is genetically engineered to fuse with human albumin, significantly prolonging its half-life. This fusion enables a slower release of the peptide reducing its degradation and allowing for less frequent injections compared to unmodified Exenatide (Rosenstock et al., 2009). In general, conjugating peptides to carrier molecules, such as proteins, antibodies, or polymers, can improve their stability, bioavailability, and targeted delivery to specific tissues or cells.

However, modifications of peptides are not always ideal, as they can also alter their biological activity, potentially reducing effectiveness or hindering interactions with their targets. To tackle these issues, a variety of innovative delivery systems have been developed (Lee and Poh, 2023).

## 5.2. Delivery systems for therapeutic peptides

A delivery system refers to a method or device designed to administer a therapeutic substance to the body in a controlled and effective manner. The goals of these systems are to optimize drug bioavailability, stability and therapeutic effectiveness while minimizing side effects and administration frequency, all without compromising the biological properties of the therapeutic agent (Sung and Kim, 2020; Blanco et al., 2015; Bruno et al., 2013).

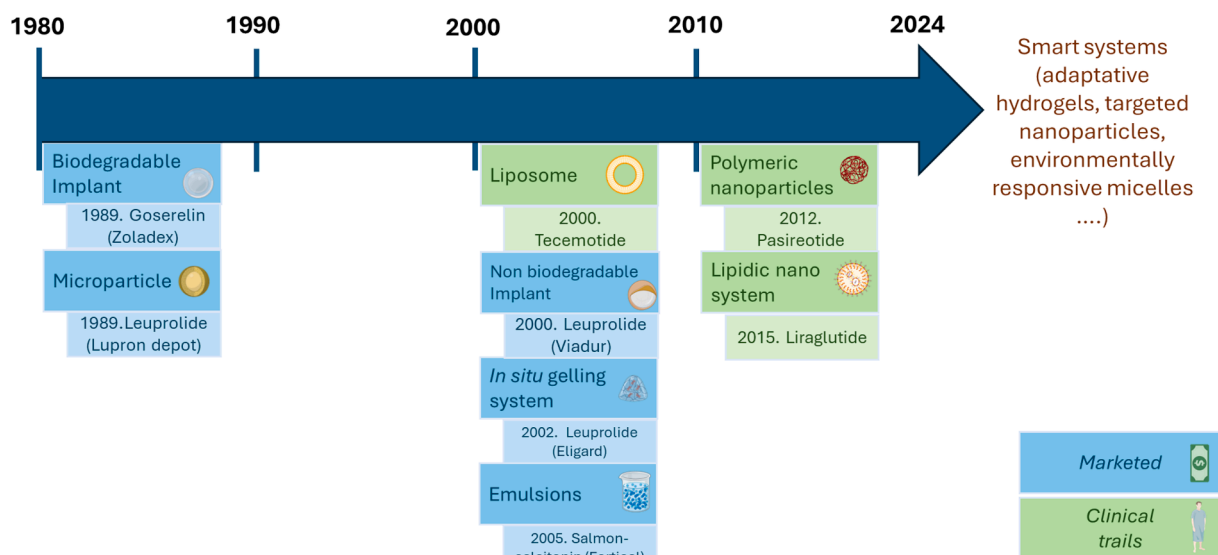
Fig. 5 illustrates the evolution of therapeutic peptide delivery systems over time, showcasing significant technological advancements since the 1980s. Some of these systems are already commercialized, offering new opportunities for therapeutic intervention, while others still remain in the research phase, highlighting the ongoing progress in this field.

### 5.2.1. Implants

A key milestone in the development of controlled-release systems for sustained peptide delivery occurred in 1989 with the launch of Zoladex, a medication designed to release goserelin for the treatment of breast and prostate cancers. Zoladex is a biodegradable implant injected subcutaneously and composed of PLGA, a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). PLGA degrades into non-toxic byproducts in aqueous media through hydrolysis of its ester linkage. The degradation rate of PLGA is influenced by different parameters, including the polymer composition, molecular weight and end groups. The gradual degradation of Zoladex leads to the controlled release of Goserelin over time (Johnson et al., 2021; Li et al., 2022). Zoladex is available in different concentrations, such as 3.6 mg, administered every 28 days, and 10.8 mg, administered every three months.

A more recent example of a degradable PLGA-based implant is Scenese, which was approved in 2019. Scenese is implanted subcutaneously every two months and releases Afamelanotide to prevent phototoxicity in adult patients with erythropoietic protoporphyria. A key difference between Scenese and other peptide PLGA products is that the Scenese implant is injected as a solid form rather than in a liquid or semi-liquid state. This advancement significantly reduces the frequency of administration compared to the peptide alone, improves patient compliance, and lays the groundwork for future innovations in drug delivery systems (Mittapelly et al., 2024; Gonella et al., 2022).

Other non-biodegradable implants have also been developed, such as Viadur, approved by the FDA in 2000. This implant, made of silicone, is injected subcutaneously to deliver Leuprolide acetate for the treatment of advanced prostate cancer. The Viadur implant is an osmotic implant that allows for the controlled release of the peptide through constant diffusion over the course of one year, much longer than Zoladex, which has a maximum release time of 3 months. Additional examples of non-biodegradable implants approved by the FDA include Vantas (approved in 2004) and Supprelin LA (approved in 2007), both of which release Histrelin over 12 months. Histrelin is used to treat advanced prostate cancer in men and central precocious puberty (CPP) in children. Since these implants do not degrade in the body, they must be removed after



**Fig. 5.** Timeline of Early FDA-Approved and Clinically Launched Therapeutic Peptide Parenteral Delivery systems. Key examples are represented on the Figure. References (Lau and Dunn, 2018; Muttenthaler et al., 2021; Center for Drug Evaluation and Research, 2023); (Wang et al., 2022; Fosgerau and Hoffmann, 2015; Zhang et al., Sep. 2020; Al Shaer et al., 2020; Kumar et al., 2024; Sharma et al., 2023); (Fetse et al., 2023) and FDA TIDES approvals were used for this Figure.

the peptide has been fully released or is no longer needed, causing discomfort for patient (Ibeanu et al., 2020; Agarwal and Rupenthal, 2013).

### 5.2.2. Microparticles

Another key milestone in the 1980 s came with the FDA approval of Lupron Depot in 1989 for intramuscular administration, marking the first resorbable PLGA-based microparticle formulation for prostate cancer. Microparticles in these formulations typically range from 1 to 100  $\mu\text{m}$  and are usually injected as a suspension, either subcutaneously or intramuscularly. For Lupron Depot, the microparticles release the peptide through two combined mechanisms: first, diffusion from the surface of the swollen microparticle (diffusion phase) followed by elution as the polymer erodes (bioerosion phase), a process that can last several months. The bioerosion of Lupron Depot involves hydrolysis, breaking down PLGA into its monomers which are then absorbed by the body and metabolized (Okada, 1997).

Lupron Depot is available in 1, 3, 4, and 6-month formulations, with respective dose of 7.5 mg, 22.5 mg, 30 mg, and 45 mg of Leuprolide Acetate. Despite the fact that the half-life of Leuprolide is only 16 min, the controlled release rate is governed by adjusting the polymer's molecular weight and the lactide-to-glycolide ratio in the PLGA. For example, the 1-month depot formulation uses a 75:25 M ratio of D,L-lactide to glycolide in the PLGA with a molecular weight of 12 kDa. The 3-month depot formulation also uses a 75:25 ratio but with a molecular weight of 14 kDa, while the 4-month depot formulation uses an 85:15 ratio with a molecular weight of 14 kDa. The 6-month depot formulation uses the same 85:15 ratio but with a molecular weight of 18 kDa (Okada, 1997).

Other examples of microspheres for the delivery of therapeutic peptides include Sandostatin LAR for the delivery of octreotide for the treatment of acromegaly, approved by the FDA in 1998 (Fløgstad et al., 1997), and Trelstar for the delivery of triptorelin for the treatment of advanced prostate cancer, approved by the FDA in 2000 (U.S Department of Health Human Services, 'Drug Approval Package: Trelstar Depot (Triptorelin Pamoate)', [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2025/Heyns, 2012](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/Heyns, 2012)). More recent examples include Bydureon for the delivery of Exenatide for the treatment of type 2 diabetes, approved by the FDA in 2012 (Deeks, 2019), and Signifor LAR for the delivery of Pasireotide for the treatment of acromegaly, approved by the FDA in 2014 (Cuevas-Ramos and Fleseriu, 2016). Despite the success of

microsphere-based formulations, there are some challenges. Indeed, the vast majority are intramuscularly (IM) administered which can cause pain, making it less ideal for patients, especially when frequent injections are required. Moreover, the manufacturing process involves the use of toxic organic solvents, which could potentially lead to safety issues (Varde and Pack, 2004).

### 5.2.3. Nanosystems

The 1990 s marked a new wave of research in controlled peptide delivery, particularly with the advent of nanoparticles which offered protection against enzymatic degradation, improved stability, and enabled targeted delivery (Blanco et al., 2015; Samec et al., 2022). Among the most widely used nanosystems are organic nanosystems like liposomes (Aronson et al., 2021; Tan et al., 2010), biodegradable polymer-based nanoparticles (Prasad et al., 2016), and micelles (Acar et al., 2017; Banerjee and Onyuksel, 2012). The mid-1990 s marked the emergence of liposomes in research, spherical vesicles made of lipid bilayers that encapsulate peptides for protection are biocompatible and can target specific tissue *in vivo* (Swaminathan and Ehrhardt, 2012). For example, Tecemotide, a liposomal formulation launched in clinical research in 2000 for intravenous delivery, is a vaccine based on the mucin-1 peptide and formulated with a synthetic lipopeptide and liposome. This vaccine was designed to induce a cellular immune response against cancer cells expressing MUC-1 and showed promising results compared to traditional injections, particularly in the treatment of non-small cell lung cancer (NSCLC). For instance, a phase III study revealed that although the vaccine did not meet its primary endpoint of improving overall survival, it demonstrated significant benefits in progression-free survival for certain patient subgroups (J.D. Patel, 2020). Although liposomes have been extensively tested in preclinical trials and have progressed to clinical trials, no therapeutic peptides are currently administered using liposomes in clinical settings. This is partly due to challenges such as stability issues, potential immunogenicity, and the complexity of large-scale production (Sonju et al., 2022).

In the 2000 s, polymeric and lipid nanoparticles gained significant popularity for stabilizing sensitive peptides and enabling sustained release. These systems were extensively explored in preclinical research for treating chronic diseases like cancer and hormonal disorders, leading to better disease management and paving the way for more practical and effective administration methods for patients. Despite some reaching clinical trials, such as Pasireotide (2012, Cushing's disease) and

Liraglutide (2015, diabetes), none of the formulations have been commercialized yet.

#### 5.2.4. *In situ* gelling system

The 2000 s also marked a transformative moment in the pharmaceutical landscape with the FDA's approval of the first sustained-release drug using an *in situ* gelling mechanism, Eligard. Approved in 2002, Eligard is a PLGA-based drug that gels upon subcutaneous injection to form a solid implant. The drug is reconstituted by physical mixing of leuprolide acetate into a polymer-solvent (N-methyl-2-pyrrolidone) system before subcutaneous injection. After injection, the solvent diffused away, allowing water to permeate the implant. This process led to phase separation and coagulation, ultimately forming the implant.

Eligard provided a prolonged, controlled release of Leuprorelin Acetate for prostate cancer treatment, improving patient compliance and outcomes (Vargason et al., 2021). Available as 1, 3, and 6-month depot injections, the polymer ratios are adjusted to regulate drug release. In a 12-month clinical trial, 99 % of patients achieved testosterone levels  $\leq 50$  ng/dl and 88 %  $\leq 20$  ng/dl with the 6 months formulation (Berges, 2007). This discovery led to a wave of preclinical research on injectable hydrogels, offering patient comfort and an optimal delivery system for therapeutic peptides (Sartor, 2003).

Both Eligard and Lupron Depot contain the same active ingredient, Leuprolide, but Eligard offers a more user-friendly formulation. Eligard is administered as a subcutaneous injection, which is generally easier and less painful for patients compared to the intramuscular injection required for Lupron Depot. Additionally, Eligard's formulation allows for a simpler and quicker preparation process, which can be more convenient for both healthcare providers and patients (Modi et al., 2024).

#### 5.2.5. Emulsions

In 2005, Fortical, a Calcitonin emulsion for intranasal administration reached the clinic. Emulsions, which are dispersions of liquid droplets within another immiscible liquid, offer robust physical protection to peptides sensitive to enzymatic or chemical degradation by encapsulating them in droplets, effectively shielding them from the external environment (Patel et al., 2014). The colloidal structure and particle size of emulsions facilitate the absorption of peptides through biological membranes (Torres-Lugo and Peppas, 2000; Morita and Yamahara, 2010).

Therapeutic peptide emulsions can be classified into various types, including water-in-oil (W/O), oil-in-water (O/W) emulsions, oil-in-oil (O/O) emulsions, and double water-in-oil-in-water (W/O/W) emulsions. For instance, octreotide, used for treating carcinoid tumors, was encapsulated in O/O emulsions (Murty et al., 2004). The results demonstrated improved peptide stability and sustained release. As for W/O/W emulsions, water droplets containing the peptide are encapsulated within oil droplets, which are then dispersed in an aqueous phase. This double encapsulation offers additional protection and controlled release. For example, trials on the encapsulation of Somatostatin, used for the treatment of endocrine disorders, into W/O/W emulsions for subcutaneous or intramuscular administration showed prolonged release and enhanced protection against enzymatic degradation (Reithmeier et al., 2001).

Current research on nanoemulsions, which are small-sized emulsions (<200 nm), highlights their enhanced stability, improved peptide delivery efficiency due to enhanced surface area, and greater bioavailability compared to conventional emulsions, making them a promising advancement in therapeutics peptides applications (Rafique et al., 2021).

#### 5.2.6. The future of therapeutic peptide delivery systems

Since the 2010 s' stimuli-responsive ("smart") drug delivery systems have gained strong attention, with peptides playing a significant role (Trimaille and Verrier, 2023). Therapeutic peptide delivery systems

offer numerous advantages, as presented in Table 2 previously. These systems notably reduce dosing frequency and decrease the degradation of active ingredients. Smart delivery systems ensure controlled and prolonged drug release, facilitate the administration of hydrophobic compounds, and improve the delivery of poorly soluble compounds. However, these systems must be biocompatible and biodegradable. Additionally, their drug payload capacity remains limited.

Stimulus-responsive systems for peptide delivery have been designed to respond to internal stimuli (e.g. osmolarity, pH, heat) as well as external stimuli (e.g. light) (Muttenhaler et al., 2021). These strategies have been applied to *in situ* gelling systems administered SC. As described previously, *in situ* gelling systems maintain the practicality of injection and gelation occur after administration leading to a sustained release of the therapeutic peptide. In contrast to PLGA-based *in situ* gelling system described above, stimulus-responsive systems avoid the need of the N-methyl-2-pyrrolidone solvent, decreasing irritation and toxicity issues. For example, preclinical research has explored new formulations, including modified chitosan and hyaluronic acid copolymers that gel upon contact with body fluids or at body temperature making them ideal for localized and controlled drug delivery. For example, a thermosensitive hydrogel based on chitosan chloride and RoY peptide (CSCI-RoY) was developed to improve angiogenesis under hypoxia after myocardial infarction. The viscosity of the CSCI-RoY solution is low when the temperature is below 34 °C (about 0.1 mPa.s) but it sharply increases at 36–37 °C. *In vitro* tests with human umbilical vein endothelial cells (HUVECs) showed that CSCI-RoY hydrogels promote the survival, proliferation, migration, and tube formation of HUVECs under hypoxia, compared to CSCI hydrogels alone. *In vivo*, in a rat model with myocardial infarction, injected CSCI-RoY hydrogels improved angiogenesis and cardiac functions (Shu et al., 2015).

Stimulus-responsive systems have also been designed to control the release of the peptide in specific tissues or at precise time. These advanced systems hold great promise for improving the precision and efficacy of drug delivery, ensuring that therapeutic agents are released in a controlled manner directly at the site of pathology, thereby minimizing side effects and enhancing treatment outcomes. For example, pH-responsive micelle was designed to release the E5 peptide, a CXCR4 receptor antagonist aimed at preventing tumor metastasis. This micelle is developed to release the peptide specifically in the tumor environment, which has a more acidic pH than healthy tissue. The encapsulation of the peptide was achieved at neutral pH through electrostatic interactions between slightly negatively charged due to the phosphate groups of the PE-PEG (phosphatidylethanolamine-polyethylene glycol) polymer micelles and the positively charged E5 peptide. A faster release of the peptide was observed at pH 5 (80 % released peptide after 24 h) compared to pH 7.4 (30 % released peptide after 24 h). This difference is attributed to electrostatic repulsion: at pH 5, the polymer becomes positively charged, leading to repulsion with the positively charged peptide and facilitating its release (Trimaille and Verrier, 2023; Fang et al., 2017). Improvements for smart delivery of therapeutic peptides has also been achieved recently with adaptative hydrogels. For example, an antimicrobial peptide (LL-37) was loaded into a chitosan hydrogel which reacts to environmental stimuli, such as acidity or the presence of bacterial enzymes, to control the release of the peptide (Yang et al., 2020). This responsiveness allows for a sustained and localized release of peptides, enhancing their therapeutic effect while reducing the need for frequent administration.

Finally, targeting delivery systems have been applied to peptides for accurate peptide delivery. Nanoparticles have been functionalized to target specific cells or tissues to overcome certain physiological barriers, improves therapeutic efficacy and decrease toxicity in various pathologies. For example, self-assembled activatable protein nanoparticles (TN-APNPs) have been designed for the delivery of the therapeutic Tat-NR2B9c peptide for the management of traumatic brain injury (TBI). To enhance the delivery of Tat-NR2B9c to the injured brain areas, their surface was modified by short targeting peptides (CAQK or CCAQK). The

conjugated nanoparticles (C-TN-APNPs and CC-TN-APNPs) showed improved delivery of Tat-NR2B9c to the injured brain areas by increasing blood–brain barrier permeability. *In vivo* studies demonstrated that CC-TN-APNPs had better circulation time, targeting ability, and therapeutic benefits compared to non-conjugated nanoparticles and represent a promising therapeutic approach for the clinical management of TBI (Wu, 2019).

The evolution of therapeutic peptide delivery systems reflects a continuous effort to enhance the efficacy, stability, and patient compliance of peptide drugs. From injectable formulations to sophisticated targeted delivery systems, each advancement brings us closer to realizing the full potential of peptide therapeutics.

Despite these advancements, challenges remain, including large-scale production biocompatibility and biodegradability of the delivery systems, risk of immunogenic reactions, and drug payload capacity. These challenges need to be addressed before these systems can be widely adopted in clinical practice.

## 6. Conclusion

Since their emergence in the 1940 s, peptides have become an important class of therapeutic agents, owing to their unique biochemical properties and versatility in treating a wide range of diseases such as diabetes, cancer, cardiovascular, and infectious diseases (Lau and Dunn, 2018; Fosgerau and Hoffmann, 2015; Craik et al., 2013). While peptides effectively complement small molecules and biologics, they face significant challenges, such as membrane impermeability and limited *in vivo* stability, largely due to their amino acid composition (Wang et al., 2022; Al Musaimi et al., 2022). Nevertheless, these obstacles have driven substantial innovation in peptide-based therapies over recent decades.

Extensive research efforts have improved peptide design, particularly through chemical modifications that enhance their stability, efficacy, and therapeutic impact (Lau and Dunn, 2018; Muttenthaler et al., 2021). What initially began as the mimicking of natural hormones has evolved into the rational design of tailor-made peptides, optimized for precise biological effects. Breakthroughs in molecular biology, peptide chemistry, and drug delivery technologies have propelled peptide-based treatments into new horizons.

Parenteral administration has become the standard for peptide delivery, ensuring stability and efficacy. The future holds exciting prospects, particularly with the emergence of advanced delivery systems. These systems offer promising potential for the controlled and prolonged release of peptides, addressing the growing demand for treatments that require sustainable and targeted administration (Lau and Dunn, 2018; Lamers, 2022).

Opportunities for innovation in peptide therapy are immense. Improving patient comfort, adopting advanced delivery systems such as *in situ* gelling, and integrating digital technologies, such as smart sensors to monitor therapies in real time, can be key factors. Additionally, combining peptide treatments for synergistic effects and adapting these therapies for specific populations, such as children and the elderly, will unlock even more potential. These advancements will be crucial in ensuring that peptides remain at the forefront of modern medicine, shaping the future of healthcare through their unparalleled therapeutic promise.

## CRediT authorship contribution statement

**E. Rosson:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **F. Lux:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **L. David:** Writing – review & editing, Funding acquisition. **Y. Godfrin:** Writing – review & editing, Funding acquisition, Conceptualization. **O. Tillement:** Writing – review &

editing, Funding acquisition, Conceptualization. **E. Thomas:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used Microsoft Copilot in order to rephrase some paragraphs. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Elise Rosson reports a relationship with Axoltis Pharma that includes: employment. Yann Godfrin reports a relationship with Axoltis Pharma that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors thank the Région Auvergne Rhône-Alpes for the R&D Booster grant HYDROPEP].

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2025.125555>.

## Data availability

Data will be made available on request.

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