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Review article

USFDA-approved parenteral peptide formulations and excipients: Industrial perspective

Samarth Kumar [a,b,*], Sachin N. Sanap [a], Milan Vasoya [a], Mayank Handa [a], Prachi Pandey [c], Ajay Khopade [a], Krutika K. Sawant [b,**]

[a] Formulation Research & Development –Non Orals, Sun Pharmaceutical Industries Ltd, Vadodara, 390020, Gujrat, India
[b] Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India
[c] Krishna School of Pharmacy & Research, KPGU, Vadodara, Gujarat, India

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ABSTRACT

Parenteral preparations are sterile and non-pyrogenic formulations designed for delivery into the human or animal body by injection, infusion, or implantation. Peptides are widely employed as therapeutic aids in the healthcare business, accounting for more than half of the pharmaceutical market, with over 100 peptides prescribed worldwide. Although FDA-approved parenteral peptide formulations have transformed significantly, they also pose significant hurdles. The most difficult task for formulation experts is to formulate the peptides into parentally deliverable dose forms while maintaining their stability, safety and efficacy. The stability of the peptide formulation is mostly influenced by the excipient used since it constitutes the majority of the formulation. The selection of acceptable excipients is critical, necessitating a thorough examination of compatibility, safety, and their impact on product stability. Furthermore, knowing peptide interactions with certain excipients and container-closure systems is critical for its safety and efficacy. This review focuses on the excipients utilized in clinically approved peptide formulations, critical challenges associated with the development of parenteral peptide formulations, safety issues, evidence on the possible interaction between peptide-excipient and packaging material, and future perspectives. Readers will be able to comprehend excipients utilized in parenteral peptide formulations and FDA-approved peptide products in great detail.

1. Introduction

Parenteral preparations are sterile formulations designed for injection, infusion, or implantation into the human or animal body [1]. Injectable products need a distinct formulation technique, as they should be sterile, pyrogen-free, and devoid of particulate matter [2]. Because the injected medicine crosses natural defense barriers, the likelihood of an adverse event is increased, or the effects are more difficult to reverse if provided via an injection rather than a non-parenteral method [3]. Peptides are extensively used as clinical aid in the healthcare industry. As defined by the US Food and Drug Administration (FDA), peptides are chains of amino acids containing a maximum of 40 monomers or less [4]. They are natural compounds found in living bodies and can be synthesized by chemical or recombinant DNA technology [5]. Very known peptides like insulin (1923) have been used to manage metabolic disorders for more than an era [6]. Currently, peptides have accommodated more than 50% of the pharmaceutical market; more than 100 peptides have been marketed globally. Looking at its growth, the modern peptide market is expected to reach USD 106 billion in the upcoming 10 years with a 6.3% compound annual growth rate (CAGR) [7].

However, formulating the peptides as parentally deliverable dosage forms and keeping their stability intact is the most challenging chore faced by formulation scientists. The stability of the peptide formulation is mainly dependent on excipients utilized in formulation, as it covers the foremost part of the formulation [8]. According to the International Pharmaceutical Excipient Council (IPEC), excipient is “any substance other than an active drug that is included in the manufacturing process or contained in finished pharmaceutical dosage form” [9]. The pharmaceutical excipients market is anticipated to grow 6% from USD 7.9 billion in 2021 to USD 10.9 billion in 2026, according to the latest report [10]. Even though excipients do not show therapeutic effects, some of

* Corresponding author. Research and Development, Sun Pharmaceutical Industries Ltd, Tandalja, Vadodara, Gujrat, 390012, India.
** Corresponding author.
E-mail addresses: Samarth.kumar@sunpharma.com (S. Kumar), k.k.sawant-pharmacy@msubaroda.ac.in (K.K. Sawant).

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them are found as toxicants in a few instances [11]. Sometimes, processing aids like solvents and other substances are used to ease production and are required to be removed from the final formulation but fail to be removed completely, which may act as a toxicant. Guidance for excipients limit use based on formulation type has been provided by the FDA [12,13]. Excipients are selected by considering several factors such as formulation type, desirable consistency, physicochemical characteristics, route of delivery, and target site [14]. Apart from this, special care has to be taken while selecting excipients for parenteral dosage forms since low bioburden and stability of excipients on terminal sterilization or aseptic conditions are essential key points to be considered by the formulator. The ideal excipient should remain stable, inert, and economical [15]. Excipients can be classified into three categories: Generally Recognized as Safe (GRAS), approved excipients which are structurally modified; and new excipients that have not been previously used in pharmaceuticals [16]. In recent years the application of quality by design (QbD) has prompted pharmaceutical industries to get a deeper comprehension of the impact of excipient functionality and performance on a therapeutic product [17]. For a substantial duration, it has been acknowledged that pharmacopoeial excipient monographs lack comprehensive coverage of excipient functionality [18]. To address this limitation, a proposal has been made for the inclusion of a general chapter on the functionality of excipients in the United States Pharmacopeia (USP).

Additionally, the European Pharmacopeia (Ph. Eur.) has incorporated a section in monographs of certain excipients on functionality-related characteristics. The recognition of excipient variability is acknowledged by the International Conference on Harmonization (ICH) Q8 and QbD [19]. There is a need for design space studies to be conducted to assess the variability of excipients and their impact on functional performance. These studies are crucial in ensuring that the established standards for excipients appropriately reflect their quality [20].

Herein, this review focuses on the excipients utilized in clinically approved peptide formulations, peptide device combinations, critical challenges associated with the development of parenteral peptide formulations, safety issues, peptide-excipient and packaging materials interaction. Readers will be able to comprehend excipients utilized in parenteral peptide formulations and FDA-approved peptide products in great detail.

2. Excipients used in parenteral peptide formulations

Peptides and other therapeutic medications are frequently formulated and stabilized using a variety of pharmaceutical excipients, which are outlined in this section. Excipients that can be used to stabilize peptides can be categorized into three categories: ions of small molecular weight (e.g. buffering agents), solutes of intermediate weight (e.g. sugars and amino acids), and larger substances (e.g. polymers). These excipients serve various purposes, such as ensuring stability, enhancing solubility, adjusting pH, and improving patient safety [16,21]. Table 1 shows some commonly used excipients in parenteral formulations and their role.

2.1. Buffering agents

Buffering agents are crucial components in parenteral formulations as they maintain the solution pH within a range that is compatible with the body's physiological pH [22]. The peptide stability and efficacy are significantly hampered by formulation pH. Therefore, proper pH control

Table 1
Excipients used in parenteral peptide formulations.

Excipients Category	Examples of excipients	General function	Demerits	Example of marketed product[a]
Buffering agents	Acetate, carbonate, citrate, triethanolamine, glycine, histidine, maleate, phosphate, succinate, tartrate	• Maintain pH of formulation	• Temperature may affect pH • During freezing and storage, crystallization and decomposition may occur	Saxenda (liraglutide] injection
Amino acids	Histidine (His), alanine (Ala), arginine (Arg), methionine (Met), aspartic acid, glycine, lysine, proline,	• His, Met is used as an antioxidant • Buffering and tonicity adjusting agents	• Can be sensitive to changes in pH • Susceptible to oxidation • Interact with the peptide itself	Daptomycin for injection
Osmolytes	Sucrose, glutamate, dextrose, NaCl, glycerol, trehalose, glycine, proline	• Protect against stress conditions such as temperature and dehydration • Use as cryoprotectants and lyoprotectants	• Generally higher amount required for stabilization • Effects of destabilizing also reported	GVOKE® (Glucagon hydrochloride)
Sugars and carbohydrates	Sucrose, glucose, lactose, fructose, trehalose, sorbitol, mannitol	• Stabilizers in solution and dry states • Tonicity adjusting agents • Use as cryoprotectants and lyoprotectants	• May interaction between reducing sugars and peptides	Cancidas® (Caspofungin acetate)
Polymers	Polyvinyl alcohol, PLGA, dextran, polyethylene glycol	• Prevent peptide adsorption • Bulking agents in freeze-dried formulations • Used as carrier/vehicle in drug delivery for temporal and spatial drug release	• Compatibility issue between polymers and peptides	Scenesse® (Afamelanotide)
Salts	Ammonium, magnesium, sodium gluconate, potassium chloride, sodium chloride	• Tonicity adjusting agents • Stability effect on peptides	• Effects are concentration-dependent • Oxidation occurs due to trace metals • Corrosive effect on metal surfaces	Daptomycin in NaCl injection,
Surfactants	Tween 20 and tween 80	• Prevent peptide adsorption • Prevent peptide surface denaturation	• Oxidation may occur • During storage chances of degradation • Micelle formation	Rezzayo™ (Rezafungin), Sandimmune® (Cyclosporine)
Chelating and anti-oxidant agents	EDTA, DTPA, ascorbic acid, glutathione, amino acids	• Bind with present metal ions • Act as scavengers for free radicals	• Peptide instability was also reported for some antioxidants	Prialt® (Ziconotide)
Preservatives	Phenol, benzyl alcohol, m-cresol	• Used in multi-dose formulations	• Inverse concentration-dependent effects on peptide destabilization vs. antimicrobial effectiveness	Leuprolide Acetate Injection

[a] May contain one or more components.

is essential for ensuring the stability and or efficacy of the drug, minimizing discomfort or irritation upon injection. The selection of buffering agents can be based on several criteria, including the buffering capacity's pH range and pKa [23]. Wider buffering capacity occurs when buffered solution has a closer value of pKa and pH. When determining the buffer concentration, the administration route must also be taken into account. While buffer selection is primarily influenced by product solubility, stability across the capacity of buffering agent and its range should also be taken into account. Buffers typically work with a dissociation constant (pKa) of ±1.0. The right buffer and concentration can be chosen with the help of these variables. Sodium acetate, sodium citrate dihydrate, glycine, maleic acid, methionine, and sodium phosphate dibasic are examples of buffer excipients that are frequently utilized. FDA-approved ANGIOMAX® (Bivalirudin, 250 mg/50 mL) is a direct thrombin inhibitor indicated for use as an anticoagulant and contains sodium acetate trihydrate as a buffering agent [24]. WEGOVY® (Semaglutide, pre-filled, single-dose pen) contains disodium phosphate dehydrate [25], whereas sodium chloride, monobasic and dibasic sodium phosphate are present in DAPTOMYCIN injection [26].

2.2. Amino acids

Amino acids can stabilize peptides by several processes, such as direct binding, preferred hydration, buffering ability, and antioxidant characteristics. Histidine, arginine, and glycine are the most often utilized amino acids as pharmaceutical excipients to stabilize peptides and proteins. Other amino acids utilized in peptide formulations include Met, aspartic acid, glutamic acid, lysine, proline, and glycine. These amino acids can act as buffers, bulking agents, stabilizers, and antioxidants. WO2001049314A2 patent reported that the addition of L-histidine to the phosphate buffer was found to effectively stabilize GLP-2 peptides, whereas the addition of arginine citrate or lysine did not effectively stabilize GLP-2 compositions. L-histidine acts as a stabilizing amino acid that increases the length of time that the GLP-2 peptide remains intact prior to degradation. Ziconotide (PRIALT®) used for the management of severe chronic pain, methionine (0.05 mg/mL) was added into final product as an antioxidant to enhance stability. DAPTOMYCIN for injection is a lipopeptide antibacterial agent available as a lyophilized powder that contains L-arginine, L-histidine, and L-isoleucine as excipients [27]. REZZAYO™ (Rezafungin, 200 mg) is an echinocandin antifungal available in a vial for reconstitution form that contains histidine as an amino acid excipient [28].

2.3. Osmolytes

Osmolytes or tonicity adjusters are essential in parenteral formulations to achieve the desired osmotic pressure in a solution, ensuring patient safety, therapeutic effectiveness, and compatibility with bodily fluids. The solution of sodium chloride (0.9 %) or dextrose (5 %) is mixed with concentrated injectable formulations to support isotonicity during infusion. When choosing tonicity agents, important aspects to take into account include the finished product osmolality (usually between 275 and 295 mOsm/kg), potential incompatibility with the active and inactive components, as well as mode of administration. Frequently utilized tonicity substances and their iso-osmotic percentage consist of sodium chloride (0.9%), potassium chloride (1%), mannitol (5%), and dextrose (5%). In addition, solvents like propylene glycol can adjust tonicity. CETROTIDE™ (Cetrorelix acetate for injection) is a synthetic decapeptide with gonadotropin-releasing hormone (GnRH) antagonistic activity that contains mannitol as a bulking as well as tonicity adjusting agent [29]. DDAVP® (Desmopressin, 4 mcg/mL) is a synthetic analogue of arginine vasopressin containing 0.9 % of sodium chloride [29].

2.4. Surfactants

Non-ionic surfactants are often added to parenteral peptide formulations to inhibit aggregation brought on by shaking or agitation. By out-competing peptide molecules for hydrophobic surfaces like air-water interfaces, non-ionic surfactants prevent peptides from unfolding at these locations. This is the primary process that underlies their ability to stabilize peptides. Polysorbate 20 and polysorbate 80 are non-ionic surfactants composed of mixtures of fatty acid esters of polyoxyethylene sorbitan with heterogeneous molecular weights and are mostly used excipients in peptide formulations. It has been demonstrated that these surfactants prevent peptides from stress caused by freezing and reconstitution, as well as agitation-induced aggregation. However, the presence of peroxides in polysorbate 20 and 80 can oxidize peptides.

Moreover, polysorbate 20 and 80 can degrade by oxidation or hydrolysis and affect the peptide stability. Their intricate behavior during membrane filtration may also make formulation development difficult, as they may form micelles at a certain concentration in solution. Lecithin (zwitterion), benzalkonium chloride (cationic), glycine (non-ionic), docusate sodium (anionic), and cremophor EL are additional surfactants that are commonly used. LUTRATE DEPOT® (Leuprolide acetate) is a gonadotropin-releasing hormone (GnRH) agonist containing polysorbate 80 as a surfactant excipient [30]. The immunosuppressive drug SANDIMMUNE® (Cyclosporine, 50 mg/mL) contains Cremophor® EL (polyoxyethylated castor oil) as an excipient [31].

2.5. Polymers

Polymers such as dextran, polyvinyl alcohol, and polyvinylpyrrolidone may be utilized as excipients during peptide and protein lyophilization [32]. Polylactic acid (PLA) or poly(lactic-*co*-glycolic acid) (PLGA) are generally used in parenteral implant formulations, which act as drug-release scaffolds [33]. SCENESSE® (Afamelanotide) is a parenteral implant containing a matrix of PLGA [34]. ZOLADEX® (Goserelin acetate) is a gonadotropin-releasing hormone (GnRH), a parenteral peptide containing D, L-lactic, and glycolic acids copolymer in implant formulation [34]. SUPPRELIN® LA (Histrelin acetate), used to treat central precocious puberty (CPP), is composed of a matrix of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, and trimethylolpropane trimethacrylate polymers [35]. Many additional water-soluble polymers are used as viscosity modifiers in parenteral formulations, such as hydroxyethyl cellulose and carboxymethyl cellulose. LUPRON DEPOT® requires dilution before administration and it contains carboxymethylcellulose sodium as a viscosity modifier excipient [36].

2.6. Antioxidants and chelators

One common degradation mechanism observed in peptide formulations during storage by metal catalysts is oxidation. Amino acids such as Met, Cys, His, and Trp are highly susceptible to oxidative degradation [37]. These oxidative reactions in peptides can be caused by tiny contaminants found in many pharmaceutical excipients, such as hydrogen peroxides and metal ions (iron, copper, or calcium). Aggregation can occur as a result of peptides binding to metal ions [38]. Pharmaceutical excipients such as sodium metabisulfite, BHA, and BHT are readily available as antioxidants. In contrast to these, ascorbic acid and glutathione (reducing agents) form mixed disulfides or oxidation with presence of certain metal ions causing peptide instability. Peptide oxidation is inhibited by metal-chelating compounds such as diethylenetriamine pentaacetic acid (DTPA) and disodium edetate (EDTA) [39]. The inclusion of amino acids like Met and His, as well as solution pH optimization and light protection, are further methods to shield peptides from metal-catalyzed oxidation.

2.7. Preservatives

Preservatives act as antimicrobial agents and are added in multi-dose formulations to prevent microbial growth. During the intended use term,

different concentrations of different preservatives are needed to guarantee antibacterial efficacy. Benzyl alcohol is the antimicrobial preservative most frequently employed in peptide formulations followed by phenol and m-cresol. It has been shown that phenolic compounds have a concentration-dependent effect on peptide aggregation [40]. Benzyl alcohol effect on the structure and stability of proteins and peptides is concentration-, temperature-, and time-dependent [41]. For this reason, a diluent containing benzyl alcohol is used for the reconstitution of lyophilized peptide formulations before injection to minimize contact time to minimize destabilizing effects. ENALAPRILAT Injection (1.25 mg/mL), BYETTA™ (Exenatide), and MIACALCIN® (Calcitonin salmon) contain benzyl alcohol, m-cresol, and phenol as preservative, respectively [42–44].

2.8. Cryoprotectants and lyoprotectants

Cryoprotectants and lyoprotectants are employed in the process of lyophilization to safeguard the peptide against adverse conditions encountered during freezing while also mitigating the stress induced during the drying phase. Cryoprotectants function by augmenting the surface tension of water molecules, hence enhancing the hydration of the active compound [45]. Lyoprotectants function through the water substitution hypothesis mechanism, which involves thermodynamic stabilization, as well as vitrification, which involves kinetic stabilization. Water substitution theory states that substituting a water molecule with lyoprotectants on active moieties' surfaces forms a hydrogen bond, preserving their structure. The active molecule or other formulation components are structurally preserved by this method. Vitrification shows that lyoprotectants immobilize and limit active component mobility and relaxation by generating a solid, glass-like structure. The excipients utilized in this context encompass sugars such as sucrose and trehalose, amino acids including glycine and arginine, as well as polyols like mannitol and sorbitol. These excipients serve the dual purpose of acting as both cryoprotectants and lyoprotectants [46]. Tables 2 and 3 show the various cryoprotectants and lyoprotectants used in commercial peptide formulations.

3. USFDA-approved parenteral peptide formulation

Peptide medications play a significant role in the contemporary pharmaceutical sector. Peptides were formerly primarily employed in hormone replacement treatment to restore the peptide level when natural synthesis was either stopped or diminished. The use of peptides is now much more widespread. The earliest use of peptide hormones in medicine dates back to the early part of the 1900s. The separation and purification of insulin in 1921 was the key event. Insulin was the first peptide to get FDA approval, and it was given as a daily injection in 1923. Peptides have been used as therapeutic agents for a long time, and their usage is growing as molecular biology, biochemistry, and medicine advances. Parenteral peptide formulations, approved by the FDA, represent a significant class of pharmaceutical products designed for direct administration into the bloodstream. Peptides are increasingly being utilized in the prevention and treatment of various medical conditions as they are having high specificity and potency. These formulations encompass a diverse range of therapeutic applications, from hormone replacement therapies and anti-cancer treatments to immunomodulatory agents and targeted therapies for chronic diseases [103]. Regulatory-approved parenteral peptide formulations undergo rigorous evaluation to ensure their safety, efficacy, and quality, with careful consideration given to factors such as excipient compatibility, stability, and manufacturing processes [104]. These innovative therapies have revolutionized healthcare by providing precise and targeted treatments, advancing the field of biopharmaceuticals, and adding benefits to the quality of life for patients with a wide array of medical conditions. Fig. 1 shows the number of approved parenteral peptides. Tables 2 and 3 show the FDA-approved parenteral peptide formulation along with used excipients, instructions, and indications.

3.1. Approved peptide-device combination products

Parenteral medication delivery has drawbacks, such as requiring competent healthcare personnel to provide the medicine. Frequently administering chronic illness medications with short half-life (small molecules/peptides) causes substantial patient non-compliance. Thus, pharmaceutical companies are developing drug delivery devices to promote patient compliance and overcome parenteral drug treatment hurdles. Combination products refer to therapeutic and diagnostic entities that integrate pharmaceuticals, devices, and biological products. These amalgamations offer enhanced treatment outcomes by meticulous medication targeting, localized delivery, and personalized therapy, hence promoting safety and efficacy. These technologies have the potential to provide significant benefits to individuals who are afflicted with severe illnesses and medical problems, including but not limited to cancer, heart disease, multiple sclerosis, and diabetes. Pre-filled syringes (PFS), autoinjector pens, and other parenteral medication devices are straightforward and patient-friendly. Most regulatory authorities have set certain standards and expectations for medication-device combination products to assure safety, convenience, reduced dosing mistakes and waste, accurate labeling, drug product sterility, and stability. Examples of FDA-approved parenteral peptide device combinations include ZEGALOGUE®, GVOKE®, BYDUREON® BCISE, BYETTA™, COPAXONE®, SOMATULINE® DEPOT, SAXENDA®, WEGOVY®, OZEMPIC®, LUTRATE DEPOT®, and LUPRON DEPOT® (Tables 2 and 3).

Regulatory bodies such as the FDA and the European Medicines Agency (EMA) have released guidelines that outline the scientific and technical information that manufacturers should take into account when producing an autoinjector pen, jet, or other injector device intended for the administration of drugs or biological formulations. The regulatory requirements for these devices vary based on their intended use, product attributes, labelling, and packaging.

3.2. Patented parenteral peptides and its formulations

Pharmaceutical companies have exclusive rights to produce and distribute patented products for a set time. After the patent expires, other companies may create and sell generic drugs, which increases market competitiveness and may lower drug prices. The patent US8921326B2, granted to Takeda Pharma, provides a comprehensive explanation of sustained release mechanisms. The composition consists of a water-soluble peptide and a polymer of lactic acid. The peptide was evenly distributed inside microcapsules composed of a lactic acid polymer, hence exhibiting prolonged release characteristics over an extended duration [105]. Another invention (US10442847B2, Zealand Pharma) is related to stable glucagon analogues and their liquid formulation. Glucagon is a 29-amino acid polypeptide used for the management of severe hypoglycemia. However, it possesses some disadvantages, including being unstable in liquid form, resulting in degradation and aggregation. However, glucagon analogue such as dasiglucagon play an important role as it is stable and available in liquid formulation [106]. Table 4 shows the patented drug substances and drug products of parenteral peptides.

3.3. Parenteral peptide formulation: critical challenges

Formulating peptides for parenteral administration presents several critical challenges due to their unique properties and sensitivities. Peptides are short amino acid chains that degrade, aggregate, and have other stability difficulties. The following section describes the critical challenges for the development of peptide formulations (Fig. 2).

Table 2
USFDA-approved parenteral peptide formulations requiring 2–8 °C storage condition[a].

Name	Application type	Brand name/ Manufacturer	Dosage Form and Strength	Route	Inactive Ingredients	No. of amino acid	Indication	Ref.
Abaloparatide	NDA	TYMLOS™ (Radius Health)	Injection: 2000 mcg/mL in a single-patient-use prefilled pen	SC	Phenol, sodium acetate trihydrate, acetic acid, and WFI	34	Postmenopausal women with osteoporosis	[47]
Afamelanotide	NDA	Scenesse® (Clinuvel, Inc.)	Implant: 16 mg of afamelanotide	SC	Poly (dl-lactide-*co*-glycolide)	13	Eythropoietic protoporphyria (EPP)	[34]
Angiotensin II	NDA	GIAPREZA (La Jolla Pharmaceutical Company)	Injection: 2.5 mg/mL per vial.	IV	Mannitol, WFI, NaOH/HCl (pH 5.5)	08	Septic or other distributive shock	[48]
Bleomycin	ANDA	Bleomycin for Injection, USP (Hospira, Inc)	Injection: 15 units or 30 units/ vial	IM, IV, SC, or Intrapleural	Sulfuric acid or NaOH	09	Cancer	[49]
Bivalirudin	NDA	Angiomax® RTU (MAIA Pharmaceuticals, Inc.)	Injection: 250 mg/50 mL in a single-dose vial.	IV	Sodium acetate trihydrate, polyethene glycol 400, NaOH, glacial acetic acid and WFI (pH 5.0–5.5)	20	Anticoagulant	[24]
Carfilzomib	NDA	Kyprolis™ (Onyx Pharma, Inc.)	Injection: 60 mg/ vial sterile lyophilized powder	IV	Sulfobutylether beta-cyclodextrin, citric acid, and NaOH (pH 3.5)	–	Treatment of patients with multiple myeloma	[50]
Caspofungin acetate	NDA	Cancidas® (Merck & Co, Inc.)	Injection: 50 or 70 mg/vial lyophilized powder	IV	Sucrose, mannitol, and glacial acetic acid, NaOH	–	Invasive *aspergillosis*	[51]
Cetrorelix acetate	NDA	Cetrotide® (EMD Serono, Inc	Injection: 0.25 mg/vial, sterile lyophilized powder	SC	Mannitol (pH 5–8)	10	Inhibition of premature LH surges in women	[29]
Calcitonin salmon	NDA	Miacalcin® (Mylan Institutional LLC)	Injection: 200 USP units/mL	SC, IM	Acetic acid, phenol, sodium acetate trihydrate, NaCl, WFI	32	Paget's disease of bone, hypercalcemia, and postmenopausal osteoporosis	[44]
Corticotropin	NDA	ACTHAR GEL (Mallinckrodt ARD LLC)	Injection: 80 USP units per mL.	IM, SC	Gelatin, phenol, cysteine NaOH/acetic acid and WFI	39	Infantile spasms, multiple sclerosis	[52]
Dalbavancin	NDA	DALVANCE (ABBVIE)	Injection: 500 mg per vial as lyophilized powder	IV	Lactose monohydrate) and mannitol	–	Acute bacterial skin and skin structure infections	[53]
Daptomycin	NDA	Daptomycin injection (Sagent Pharmaceuticals)	Injection: 350 mg/vial lyophilized powder	IV	NaOH (pH 4.0 to 5.0)	13	Skin and skin structure infections	[27]
Dasiglucagon	NDA	Zegalogue® Zealand Pharma A/S	Injection: 0.6 mg/0.6 mL single-dose autoinjector and prefilled syringe	SC	Tromethamine, NaCl, WFI. HCl and NaOH (pH 6.5)	29	Severe hypoglycemia	[54]
Desmopressin	NDA	DDAVP® (Ferring Pharma. Inc.)	Injection: 40 mcg/10 mL in a multiple-dose vial	IV/SC	NaCl, chlorobutanol, HCl, and WFI	09	Central Diabetes Insipidus, Hemophilia A, von Willebrand's disease (Type I)	[55]
Eptifibatide	ANDA	Eptifibatide injection (Sagent Pharmaceuticals)	Injection: 2, 0.75 and 2 mg/mL per vial for bolus, infusion and infusion, respectively	IV	Citric acid and NaOH (pH 5.35)	06	Acute coronary syndrome (ACS) and patients undergoing PCI	[56]
Etelcalcetide	NDA	Parsabiv™ (KAI Pharma., Inc)	Injection: 2.5 mg/0.5 mL, 5 mg/mL, and 10 mg/2 mL solution per vial	IV	NaCl, succinic acid, HCl (pH 3.3)	08	Secondary hyperparathyroidism (HPT)	[57]
Exenatide	NDA	Bydureon® Bcise™ (AstraZeneca Pharmaceuticals LP)	Injectable: 2 mg/ 0.85 mL single-dose autoinjector	SC	Poly (D, l-lactide-*co*-glycolide), sucrose, medium chain triglycerides (MCT)	39	Type 2 diabetes mellitus	[43, 58]
		Byetta™ (AstraZeneca	Injection: 250 mcg/mL, 2.4 mL, pen-injector		Metacresol, mannitol, glacial acetic acid, sodium acetate trihydrate, WFI (pH 4.5)			

(*continued on next page*)

Table 2 (*continued*)

Name	Application type	Brand name/ Manufacturer	Dosage Form and Strength	Route	Inactive Ingredients	No. of amino acid	Indication	Ref.
		Pharmaceuticals LP)						
Glatiramer acetate	NDA	Copaxone® (Teva Neuroscience, Inc.)	Injection: 20 mg/ mL in a prefilled syringe	SC	Mannitol (pH 5.5 to 7.0)	04	Multiple sclerosis	[59]
Histrelin acetate	NDA	Supprelin® LA (Endo Pharmaceuticals Inc.)	Implant: (50 mg) delivers 65 mcg/ day over 12 months.	SC	Stearic acid, 2-hydroxyethyl methacrylate, 2-hydroxy-propyl methacrylate, benzoin methyl ether, Triton X-100 trimethylolpropane trimethacrylate, Perkadox-16, NaCl solution	09	Treatment of children with central precocious puberty (CPP)	[35]
Lanreotide	NDA	Lanreotide injection (Cipla USA Inc.) Somatuline® Depot (Ipsen Pharma Biotech)	Injection: 60 mg/ 0.2 mL, 90 mg/ 0.3 mL, and 120mg/0.5 mL single-dose prefilled syringes	SC	WFI and acetic acid	08	Acromegaly	[60]
Liraglutide	NDA	Saxenda injection (Novo Nordisk A/ S)	Injection: pre-filled, multi-dose pen (6 mg/mL, 3 mL)	SC	Propylene glycol, Disodium phosphate dihydrate, phenol, WFI	30	Chronic weight management (Novo Nordisk, 2014)	[61]
Octreotide acetate	NDA	Sandostatin LAR® Depot (Novartis)	Injection: 10, 20 or 30 per vial	IM	Glucose star polymer, D,L-lactic and glycolic acids copolymer and mannitol	08	Acromegaly, Carcinoid Tumors, Vasoactive Intestinal Peptide Tumors	[62, 63]
		Sandostatin (Novartis)	Injection: 50, 100, and 500 mcg per ampoule		Lactic acid, mannitol, sodium bicarbonate, WFI (pH 4.2)			
Pasireotide	NDA	SIGNIFOR® LAR (Recordati Rare)	Injection: 20, 40, and 60 mg per vial as lyophilized powder	IM	Poly(d,l-lactide-*co*-glycolide), The diluent contains mannitol, carboxymethylcellulose sodium, poloxamer 188, WFI	06	Acromegaly	[64]
Pegcetacoplan	NDA	SYFOVRE ™ (Apellis Pharmaceuticals, Inc.)	Injection: 150 mg/mL in a single-dose vial	Intravitreal	Trehalose dehydrate, glacial acetic acid, sodium acetate trihydrate, WFI, NaOH/ glacial acetic acid (pH 5.0.)	15	Geographic atrophy (GA)	[65]
Pramlintide	NDA	SYMLIN (ASTRAZENECA AB)	Injection: 0.6 mg/mL	SC	Metacresol, D-mannitol, acetic acid, sodium acetate (pH 4.0)	37	Diabetes	[66]
Quinupristin and Dalfopristin	NDA	Synercid® I.V. (King Pharms)	Injection: 500 mg (150mg/350 mg) per vial	IV	–		Antibacterial	[67]
Semaglutide	NDA	Wegovy® (Novo Nordisk A/S)	Injection: 0.25, 0.5, 1, 1.7 and 2.4 mg prefilled injection	SC	Disodium phosphate dihydrate, NaCl, WFI, HCl or NaOH (pH 7.4)	31	Chronic weight management	[25]
		Ozempic® (Novo Nordisk A/S)	Injection: 2 mg/ 1.5 mL Single-patient-use pen		Disodium phosphate dihydrate, propylene glycol, Phenol, WFI, HCl or NaOH (pH 7.4)		Type 2 diabetes mellitus	[68]
Teduglutide	NDA	GATTEX (Takeda)	Injection: 5 mg/ vial as lyophilized powder	SC	l-histidine, mannitol, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate	33	Short Bowel Syndrome (SBS)	[69]
Terlipressin	NDA	Terlivaz® (Mallinckrodt Hospital Products Inc.)	Injection: 0.85 mg/vial as a lyophilized powder	IV	Mannitol, glacial acetic acid, and NaOH	12	Hepatorenal syndrome	[70]
Teriparatide	NDA	FORTEO™ (Eli Lilly and Company)	Injection: 250 mcg/mL	SC	Glacial acetic acid, sodium acetate (anhydrous), mannitol, Metacresol, WFI, HCl/NaOH (pH 4)	84	Postmenopausal women with osteoporosis	[71]
Tirzepatide	NDA	Mounjaro™ (Eli Lilly USA, LLC)	Injection: 2.5, 5, 7.5, 10 mg, 12.5, or 15 mg per 0.5 mL in a single-dose pen	SC	NaCl, sodium phosphate dibasic heptahydrate, and WFI. HCl and NaOH (pH (6.5–7.5)	39	Type 2 diabetes mellitus	[72]
Telavancin hydrochloride	NDA	Vibativ® (Cumberland Pharma Inc.)	Injection: 750 mg/vial	IV	Hydroxypropylbetadex, mannitol, NaOH and HCl (pH 4.0 to 5.0)	–	Skin and skin structure infections, bacterial pneumonia	[73]
Vasopressin	NDA	Vasopressin injection	Injection: 20 units per mL	IV	Chlorobutanol, NaCl, WFI, and acetic acid (pH 3.5)	09	Vasodilatory shock	[74]

(*continued on next page*)

Table 2 (*continued*)

Name	Application type	Brand name/ Manufacturer	Dosage Form and Strength	Route	Inactive Ingredients	No. of amino acid	Indication	Ref.
		(American Regent, Inc.)						
Vosoritide	NDA	Voxzogo® (BioMarin Pharma Inc)	Injection: 0.4, 0.56, or 1.2 mg lyophilized powder	SC	Trehalose dihydrate, mannitol, sodium citrate dihydrate, methionine, citric acid monohydrate, and polysorbate 80	39	Achondroplasia	[75]
Ziconotide	NDA	Prialt® (Elan Pharma, Inc	Injection: 100 mcg/mL and 25 mcg/mL	Intrathecal (IT)	l-methionine and NaCl (pH 4.0–5.0)	25	Management of severe chronic pain	[76]

[a] The data was collected from USFDA official website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

3.4. Stability and degradation

Stability and degradation are important for formulating parenteral peptides because peptides degrade easily, compromising their efficiency and safety [139]. Successful parenteral peptide formulations need knowledge of peptide degradation processes and stabilization techniques. Chemical, enzymatic, and physical degradation are the main mechanisms of peptide degradation (Fig. 3) [140,141]. Chemical degradation processes include hydrolysis (e.g. Insulin, Vasopressin, Leuprolide acetate); oxidation (e.g. Glucagon, Oxytocin, Vasopressin, Enkephalins, Calcitonin, Parathyroid hormone (PTH); deamidation (e.g. Glucagon, Goserelin, Lantus), and racemization (e.g. Leucine Enkephalin, Leuprolide, Somatostatin analogues) [142]. Peptides can be broken down by proteolytic enzymes in enzymatic degradation, including proteases, peptidases, and endopeptidases. Exenatide, Liraglutide, Leuprolide, Goserelin, Oxytocin, Enkephalins, and Insulin are some examples that undergo enzymatic degradations [143]. Whereas in physical degradation, physical factors such as temperature (e.g. Insulin, Enfuvirtide, Exenatide, and Liraglutide), agitation (e.g. Oxytocin, Leuprolide acetate, Desmopressin, Somatostatin analogues) and light (e.g. Oxytocin, Vasopressin, Calcitonin, Octreotide) can cause degradation by promoting aggregation or denaturation of peptides [144]. Insulin is highly sensitive to temperature and agitation and can undergo aggregation, leading to a loss of activity and unpredictable absorption kinetics [145]. GLP-1 analogues like exenatide require storage at refrigerated temperatures to maintain stability due to their sensitivity to heat and potential aggregation [146].

3.5. Aggregation

Aggregation is a significant challenge in the formulation and stability of parenteral peptide formulations [142]. Peptide aggregation is a prevalent cause of instability, and in the manufacture of therapeutic peptides, it might make the product unsuitable for release. It refers to the process by which individual peptide molecules come together to form larger structures, such as dimers, oligomers, or even insoluble particles. The primary, secondary, hydrophobic interactions and electrostatic interactions are the main mechanisms for peptide aggregation [147]. Peptide aggregation can occur due to interactions between amino acid residues within the peptide chain [148]. Certain amino acid sequences, particularly hydrophobic regions, are more prone to self-association. Peptide secondary structures, such as beta-sheet formation, can promote aggregation by bringing individual peptide chains together. Hydrophobic interactions between exposed hydrophobic amino acids on different peptide molecules can drive aggregation as peptides attempt to minimize their exposure to the aqueous environment [149]. Electrostatic interactions, including charge-charge repulsions or attractions, can influence peptide aggregation. Peptides with charged residues may form aggregates through electrostatic interactions [150]. Aggregated peptides can trigger an immune response, leading to the formation of antibodies against the peptide [151]. This reduces therapeutic benefits and raises patient safety issues. Aggregated peptides enhance formulation viscosity, making fine-gauge needle injections harder. It might cause patient pain and compromise dose accuracy. Glucagon and insulin regulate blood glucose levels and are administered to individuals with diabetes to address hypoglycemia and hyperglycemia, respectively. While insulin remains stable for several days in its solution form, glucagon quickly forms fibrils when exposed to the acidic pH necessary for solubility. Glucagon, with an isoelectric point of 7.1, exhibits insolubility in water under physiological pH conditions (pH 4–8). When the pH is 3 or below, glucagon is initially able to dissolve, but after a few hours, it will come together to create a gel. The gelled glucagon primarily consists of β-sheets or fibril structures and has the potential to obstruct the thin tubing of an infusion set [152]. Hence, injecting glucagon fibrils or gels is considered hazardous. Therefore, glucagon is produced as a lyophilized powder and must be reconstituted in an acidic solution just before use. Octreotide, a somatostatin analogue used to treat acromegaly and neuroendocrine tumors may aggregate, especially in long-acting depot formulations, which causes injection site pain, decreased medication availability, and altered pharmacokinetics, impacting therapeutic outcomes [153].

3.6. pH sensitivity

The pH sensitivity is another critical factor in the stability of parenteral peptides, as it can significantly impact the drug's stability, solubility, and efficacy. Many peptides have specific pH requirements for stability, and deviations from these conditions can lead to degradation. Some peptides require acidic or alkaline conditions for stability [154]. Insulin is a well-known example of a pH-sensitive peptide. It is most stable at slightly acidic pH conditions (pH around 3.5 to 4.5) [155]. Deviations from this pH range can result in insulin aggregation and reduced effectiveness. Enfuvirtide is an antiretroviral peptide used in the treatment of HIV that must be reconstituted in a specific buffer solution (pH 4) before administration [156]. Liraglutide is used for diabetes and obesity treatment needs to be formulated at a slightly acidic pH to ensure stability and effectiveness [157]. Whereas, US9925233B2 patent shows that the highest stability (assay) of vasopressin were achieved in range of pH 3.4–3.6 with minimum impurities profile.

3.7. Viscosity

Viscosity is an important parameter in parenteral products, including peptide formulations. Viscosity can have a significant impact on the ease of administration, patient comfort, and the performance of the formulation [158]. Viscosity modifiers or thickening agents, are added to parenteral formulations to adjust and control their viscosity, flow characteristics and stability of the formulation. Hydroxyethyl cellulose (HEC), methylcellulose, carbomer, and poloxamers (pluronics) are some examples of viscosity modifiers used in parenteral formulations. FORTEO® is a peptide-based product that contains teriparatide, a synthetic version of parathyroid hormone used for the treatment of osteoporosis

Table 3
USFDA-approved parenteral peptide formulations other than 2–8 °C storage conditions[a].

Name	Application type	Brand name/ Manufacturer	Dosage Form and Strength	Route	Inactive Ingredients	No. of amino acid	Storage	Indication	Ref.
Anidulafungin	NDA	ERAXIS™ (Vicuron Holdings)	Injection: 50, 100 mg/vial lyophilized powder	IV	Fructose, mannitol, polysorbate 80, tartaric acid, HCl/NaOH	–	25 °C	Fungal infections	[77]
Bremelanotide acetate	NDA	Vyleesi® (Palatin Technologies)	Injection: 1.75 mg/0.3 mL solution	SC	Glycerin, SWFI, HCl, NaOH	07	25 °C	Premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)	[78]
Caspofungin acetate	NDA	Caspofungin acetate for injection (Fresenius Kabi, USA)	Injection: 50 or 70 mg/vial lyophilized powder	IV	Arginine and HCl/NaOH	–	20–25 °C	Treatment of candidemia	[79]
Cosyntropin	NDA	Cortrosyn® (Amphastar Pharmaceuticals, Inc.)	Injection: 0.25 mg/vial	IM/IV	Mannitol, NaOH and Glacial acetic acid	39	15–30 °C	Aadrenocortical insufficiency	[80]
Cyclosporine	NDA	Sandimmune® (Novartis Pharma)	Injection: 50 mg/mL	IV	Cremophor EL (polyoxyethylated castor oil), alcohol, nitrogen	11	Below 30 °C	Prevention of organ rejection in kidneys, liver and heart allogeneic transplants	[31]
Daptomycin	NDA	Daptomycin for injection (Xellia Pharma. USA, LLC)	Injection: 350 mg and 500 mg/ vial lyophilized powder	IV	l-arginine, l-histidine, l-isoleucine HCl (pH 5.7–6.7)	13	20–25 °C	Skin and skin structure infections and *Staphylococcus aureus*	[26, 27,
		Daptomycin injection (Hospira, Inc.)			Citric acid and NaOH		2–25 °C	bacteremia	81]
		Daptomycin in NaCl injection, (Baxter Healthcare Corporation)	Injection: 350 mg/50 mL, 500 mg/50 mL, 700 mg/100 mL, and 1000 mg/100 mL in single-dose GALAXY Container		NaCl, monobasic sodium phosphate, dibasic sodium phosphate, HCl, NaOH, WFI		−20 °C		
Degarelix acetate	NDA	Firmagon ® (Ferring Pharmaceuticals Inc)	Injection: 120 mg and 80 mg per vial	SC	Mannitol	12	25 °C	Advanced prostate cancer	[82]
Difelikefalin	NDA	Korsuva™ (Cara Therapeutics, Inc)	Injection: 65 μg/1.3 mL (50 μg/mL)	IV	Acetic acid, sodium acetate trihydrate, NaCl, and WFI (pH 4.5)	–	20–25 °C	Pruritus associated with chronic kidney disease	[83]
Enalaprilat	ANDA	Enalaprilat Injection (Dr. Reddys Laboratories Inc)	Injection: 1.25 mg/mL	IV	NaCl, NaOH, WFI, benzyl alcohol	–	20–25 °C	Hypertension	[42]
Enfuvirtide	NDA	Fuzeon™ (Hoffmann-La Roche Inc.)	Injection: 90 mg/mL	SC	Mannitol, sodium carbonate (anhydrous), NaOH and HCl (pH 9.0)	36	25 °C	HIV-1 infection	[84]
Ganirelix acetate	NDA	Antagon™ (Organon Inc.)	Injection: 250 μg/0.5 mL	SC	Glacial acetic acid, mannitol, WFI, acetic acid and NaOH (pH 5.0)	09	25 °C	Inhibition of premature LH surges in women	[85]
Glucagon hydrochloride	NDA	GlucaGen® (NoVo Nordick)	Injection: 1 mg/vial	SC/ IM/IV	Lactose monohydrate, HCl and NaOH (pH 2.5–3.5)	29	20–25 °C	Antihypoglycemic agent and a gastrointestinal motility inhibitor	[86, 87]
		Glucagon for Injection (Eli Lilly and Company)	Injection: 1 mg/vial		Lactose monohydrate, HCl. The diluent contains glycerin, WFI, and HCl				
		GVOKE® (Xeris Pharma., Inc)	Injection: 0.5 mg/0.1 mL and 1 mg/0.2 mL pre-filled auto-injector and pre-filled syringe	SC	Trehalose dihydrate, sulfuric acid, dimethyl sulfoxide diluent			Severe hypoglycemia	[88]
Goserelin Acetate	NDA	Zoladex® (TerSera Therapeutics LLC)	Implant 10.8 mg	SC	D, L-lactic and glycolic acids copolymer	09	25 °C	Carcinoma of the prostate	[89]
Human secretin	NDA	Chirhostim® (ChiRhoClin, Inc)	Injection: 16 mcg or 40 mcg/ vial as a lyophilized powder	IV	l-cysteine hydrochloride, mannitol, NaCl (pH 3–6.5)	27	−20 °C	Stimulation of pancreatic secretions, gastrin secretion	[90]
Dactinomycin	NDA	Cosmegen® (Recordati Rare Diseases, Inc.)	Injection: 500 mcg/vial as a lyophilized powder	IV	Mannitol	–	20 - 25 °C	Wilms tumor, metastatic, rhabdomyosarcoma, Ewing sarcoma, nonseminomatous testicular cancer	[91]
Icatibant	NDA	Firazyr® (Shire Orphan Therapies, Inc.)	Injection: 10 mg/mL	SC	NaCl, glacial acetic acid, NaOH, WFI (pH of 5.5)	10	2–25 °C	Acute attacks of hereditary angioedema (HAE)	[92]
Leuprolide acetate	NDA	Lutrate depot® (GP-PHARM, S.A.)	Injection: 22.5 mg/vial as a kit with a prefilled syringe containing diluent	IM	Polylactic acid, triethyl citrate, polysorbate 80, mannitol, and carmellose sodium. Diluent contains mannitol, WFI, NaOH and HCl to control pH	09	20–25 °C	Advanced prostate cancer	[30, 36, 93]

(*continued on next page*)

Table 3 (*continued*)

Name	Application type	Brand name/ Manufacturer	Dosage Form and Strength	Route	Inactive Ingredients	No. of amino acid	Storage	Indication	Ref.
	ANDA	Leuprolide Acetate Injection (Sun Pharmaceutical Industries, Inc.)	Injection, 14 mg/2.8 mL	SC	NaCl, benzyl alcohol, WFI, NaOH, glacial acetic acid (pH 4.5 to 6.5)				
	NDA	Lupron depot® (AbbVie Inc.)	Injection: 7.5 mg, 22.5 mg, 30 mg, and 45 mg injections in a kit	IM	Purified gelatin, DL-lactic and glycolic acids copolymer, and D-mannitol. Diluent contains carboxymethylcellulose sodium, D-mannitol, polysorbate 80, WFI, glacial acetic acid				
Oritavancin	NDA	KIMYRSA™ (MELINTA THERAP)	Injection: 1200 mg of lyophilized powder	IV	Hydroxypropyl-β-cyclodextrin (HPβCD), mannitol, phosphoric acid or NaOH (pH 4.0–6.0)	–	20–25 °C	Antibacterial	[94]
Oxytocin	NDA	Pitocin® (Par Pharmaceutical, Inc)	10 USP units/mL	IV/IM	Chlorobutanol, acetic acid, ammonium acetate (pH 3.5)	09	20–25 °C	Uterine contractions	[95]
Pasireotide diaspartate	NDA	SIGNIFOR (RECORDATI RARE)	Injection: 0.3, 0.6, and 0.9 mg/mL in a single-dose ampule	SC	Mannitol, tartaric acid, sodium hydroxide, WFI (pH 4.2)	06	25 °C	Cushing's disease	[96]
Rezafungin	NDA	Rezzayo™ (Patheon Italia S.p.A)	Injection: 200 mg/vial as lyophilized powder	IV	Histidine, mannitol, polysorbate 80, HCl and NaOH	–	5–25 °C	Candidemia and invasive candidiasis	[28]
Romidepsin	NDA	ISTODAX® (BRISTOL-MYERS)	Injection: 10 mg +2 mL diluents	IV	Povidone. Diluent contains propylene glycol dehydrated alcohol	04	20–25 °C	Cutaneous T-cell lymphoma	[97]
Triptorelin	NDA	TRIPTODUR (Arbor Pharmaceuticals, LLC)	Injectable suspension: 22.5 mg/vial lyophilized powder	IM	PLGA, mannitol, carboxymethylcellulose sodium, and polysorbate 80	09	20–25 °C	Central precocious puberty	[98]
		TRELSTAR™ DEPOT (Debio Recherche)	Injectable suspension, 3.75 mg				25 °C	Advanced prostate cancer	[99]
Vancomycin	NDA	Vancomycin HCl (Baxtar)	Infusion: Premixed 100 mL, 150 mL, or 200 mL solution containing 500 mg, 750 mg, or 1 g Vancomycin HCl	IV	Dextrose hydrous, sodium chloride (pH 3.0–5.0)	07	−20 °C	Antibacterial agent	[100, 101]
		Vancomycin HCl (MYLAN LABS LTD)	Injection: 250 mg, 750 mg, 1.25 g, or 1.5 g per vial		–		20–25 °C		
Vasopressin	NDA	Vasostrict™ (Par Pharmaceutical Companies, Inc)	Injection: 20 units/mL	IV	Chlorobutanol, WFI, acetic acid (pH 3.4–3.6)	09	15–25 °C	Vasodilatory shock	[102]

[a] The data was collected from USFDA official website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

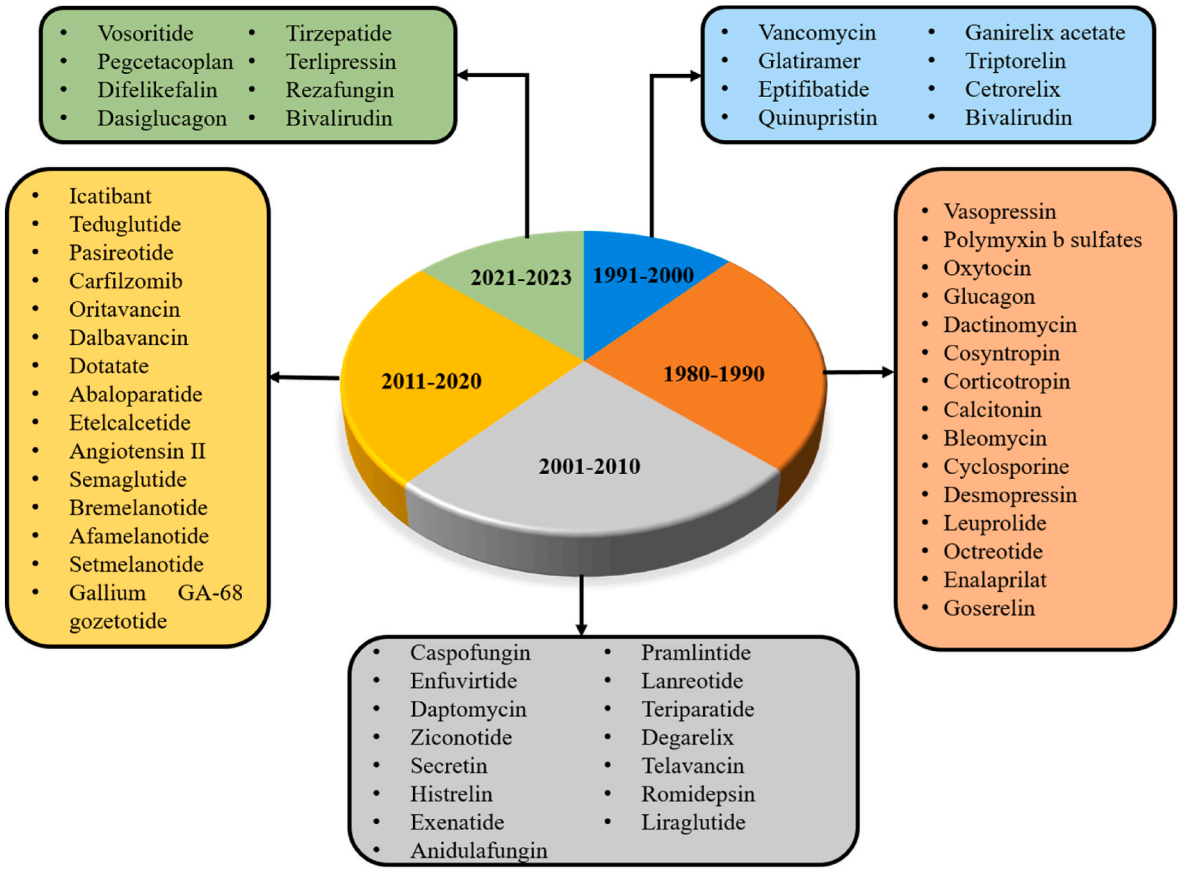

Fig. 1. Number of approved parenteral peptides with their timeline.

approved by FDA in 2002 [159]. It is formulated with a specific viscosity to ensure easy subcutaneous injection using a pen device. The formulation includes ingredients to adjust the viscosity for optimal patient comfort and dosing precision [160].

3.8. Solubility

The stability and efficacy of parenteral peptides depend on their solubility in a solvent or buffer. Due to limited solubility or aggregation concerns, more than 90% of peptide medication candidates are abandoned during preclinical or clinical studies [161]. Proper solubility ensures correct dosage, bioavailability, and patient safety. For poorly soluble peptides, co-solvents such as propylene glycol or ethanol may be added to the formulation to improve their dispersibility and homogeneity [162]. Octreotide acetate, used in conditions like acromegaly, has poor aqueous solubility. It is formulated with co-solvents like acetic acid and mannitol to improve solubility and stability. Solubilizing excipients such as cyclodextrins, surfactants, or complexing agents can be employed to improve peptide solubility [163]. These excipients can interact with the hydrophobic regions of the peptide, increasing its solubility in water. Kyprolis™ (Carfilzomib) 60 mg/vial sterile lyophilized powder contains sulfobutylether beta-cyclodextrin to enhance solubility. The presence of hydroxypropylbetadex in the formulation of VIBATIV® at a ratio of 1:10 reduces the incidence and severity of the changes due to telavancin and attenuates the glycopeptides-like toxicity of telavancin [73].

3.9. Dosage precision

Accurate dosage is needed to ensure that patients obtain the desired treatment without underdosing or overdosing. To minimize side effects and guarantee treatment effectiveness, precise dosage is necessary as many peptides have a low therapeutic index. Potent opioid peptide fentanyl, variations in dosage administration might cause respiratory depression or insufficient pain relief. Therefore, it is administered using specialized devices like patient-controlled analgesia (PCA) pumps, which allows patient compliance as it can be self-administer and gives small, predetermined doses [164]. GLP-1 analogues, such as liraglutide that are used to manage diabetes and obesity, precise dosing is crucial to regulate blood glucose levels effectively as inaccurate dosing can result in insufficient glycemic control or an increased risk of hypoglycemia. Merritt D *et al.* studied the dose accuracy and injection force of disposable pens of pramlintide for the treatment of diabetes and reported that the high dose accuracy and low injection force were observed for the 60 and 120 μg pens under a variety of conditions [165].

3.10. Lyophilization (freeze-drying)

Lyophilization, commonly known as freeze-drying, is a pharmaceutical formulation technique used to enhance the stability, shelf life, and reconstitution properties of certain drugs, including peptides, proteins, and other heat-sensitive compounds. It involves the removal of water from a product while preserving its biological activity and structure. The advantages of lyophilizations include reducing the risk of chemical and physical degradation reactions, such as hydrolysis, aggregation, or oxidation, which can occur in the presence of water and at higher temperatures. This is especially crucial for peptides that are sensitive to these reactions. The removal of water prevents microbial growth and enzymatic degradation, contributing to longer shelf life. Lyophilized peptides can be easily reconstituted with a suitable diluent before administration, providing consistent dosing and ease of use. In lyophilized protein and peptide products, a prevalent issue arises from pH alterations resulting from the crystallization of buffer components, leading to the loss of active ingredients. Moreover, non-invasively

Table 4
Patented drug substances and drug products of parenteral peptides.

Name	Patent No.	Expiration	DS/ DP	Applicant/Assignee/Country	Title of innovation	Ref.
Afamelanotide	US8334265B2	03-11-2029	–	Clinuvel Pharmaceuticals Limited, Melbourne, Victoria (AU)	Method of treatment of photodermatoses	[107]
	US10076555B2	02-11-2025	–	Clinuvel Pharmaceuticals Limited, Melbourne, Victoria (AU)	Methods of inducing melanogenesis in a subject	[108]
Bivalirudin	US7582727B1	07/27/2028	DP	The Medicines Company, Parsippany, NJ (US)	Pharmaceutical formulations of bivalirudin and processes of making the same	[109]
Carfilzomib	US7232818B2	04/14/2025	DS + DP	Onyx Therapeutics Inc., South San Francisco, CA (US)	Compounds for enzyme inhibition	[110]
	US7417042B2	07/20/2026	DS + DP	Onyx Therapeutics Inc., South San Francisco, CA (US)	Compounds for enzyme inhibition	[111]
	US7737112B2	12-07-2027	DP	Onyx Therapeutics Inc., South San Francisco, CA (US)	Compounds for enzyme inhibition	[112]
	US9493582B2	02/27/2033	DP	Cydex Pharmaceuticals, Inc., San Diego, CA (US)	Alkylated cyclodextrin compositions and processes for preparing and using the same	[113]
Daptomycin	US9655946B2	09-11-2033	DP	Hospira Australia Pvt Ltd., Victoria (AU)	Daptomycin formulations and uses thereof	[114]
Dasiglucagon	US10442847B2	02-03-2035	DS + DP	Zealand Pharma A/S, Søborg (DK)	Glucagon analogues	[106]
Etelcalcetide	US8377880B2	07/29/2030	DS + DP	KAI Pharmaceuticals, Inc., South San Francisco, CA (US)	Therapeutic agents for reducing parathyroid hormone levels	[115]
	US11162500B2	06/27/2034	DP	Amgen Inc., Thousand Oaks, CA (US)	Stable liquid formulation of AMG 416 (etelcalcetide)	[116]
Exenatide	US6515117B2	10-04-2025	DS + DP	Bristol-Myers Squibb Company, Princeton, NJ (US)	C-aryl glucoside SGLT2 inhibitors and method	[117]
	US7456254B2	06/30/2025	DP	Alkermes, Inc., Cambridge, MA (US)	Polymer-based sustained-release device	[118]
Histrelin acetate	US8062652B2	06/16/2026	–	Endo Pharmaceuticals Solutions Inc., Chadds Ford, PA (US)	Compositions and methods for treating precocious puberty	[119]
Liraglutide	US7762994B2	05/23/2024	DP	Novo Nordisk A/S, Bagsvaerd (DK)	Needle mounting system and a method for mounting a needle assembly	[120]
	US8114833B2	08/13/2025	DP	Novo Nordisk A/S, Bagsvaerd (DK)	Propylene glycol-containing peptide formulations which are optimal for production and for use in injection devices	[121]
	US9132239B2	02-01-2032	DP	Novo Nordisk A/S, Bagsvaerd (DK)	Dial-down mechanism for wind-up pen	[122]
Semaglutide	US8129343B2	12-05-2031	DS + DP	Novo Nordisk A/S, Bagsvaerd (DK)	Acylated GLP-1 compounds	[123]
	US10376652B2	01/20/2026	DP	Novo Nordisk A/S, Bagsvaerd (DK)	Automatic injection device with a top-release mechanism	[124]
Tirzepatide	US8734394B2	02/24/2031	DP	Eli Lilly and Company, Indianapolis, IN (US)	Automatic injection device with delay mechanism including a dual-functioning biasing member	[125]
	US9474780B2	01-05-2036	DS + DP	Eli Lilly and Company, Indianapolis, IN (US)	GIP and GLP-1 co-agonist compounds	[126]
	US11357820B2	06/14/2039	DP	Eli Lilly and Company, Indianapolis, IN (US)	GIP/GLP1 agonist compositions	[127]
Telavancin hydrochloride	US6635618B2	09-11-2023	DS + DP	Cumberland Pharmaceuticals Inc	Glycopeptide phosphonate derivatives	[128]
	US7531623B2	01-01-2027	DS	Cumberland Pharmaceuticals Inc	Hydrochloride salts of a glycopeptide phosphonate derivative	[129]
Vasopressin	US9919026B2	01/30/2035	DP	Par Pharmaceutical, Inc., Chestnut Ridge, NY (US)	Vasopressin formulations for use in treatment of hypotension	[130]
Vosoritide	US8198242B2	06-11-2030	DS + DP	Biomarin Pharmaceutical Inc., Novato, CA (US)	Variants of C-type natriuretic peptide	[131]
	US9907834B2	08-01-2036	DP	Biomarin Pharmaceutical Inc., Novato, CA (US)	Use of C-type natriuretic peptide variants to treat skeletal dysplasia	[132]
Ziconotide	US8653033B2	10-01-2024	–	Jazz Pharmaceuticals International Limited, Hamilton (BM)	Method for administering omega-conopeptide	[133]
Bremelanotide acetate	US6794489B2	06/28/2025	DS + DP	Palatin Technologies, Inc., Cranbury, NJ (US)	Compositions and methods for treatment of sexual dysfunction	[134]
	US11590209B2	04/29/2041	DP	Palatin Technologies, Inc., Cranbury, NJ (US)	Use of bremelanotide in patients with controlled hypertension	[135]
Caspofungin acetate	US9636407B2	12/21/2032	DP	Fresenius Kabi usa, LLC, Lake Zurich, IL (US)	Caspofungin acetate formulations	[136]
Daptomycin	US9655946B2	09-11-2033	DP	Hospira Australia Pty Ltd., Victoria (AU)	Daptomycin formulations and uses thereof	[114]
Difelikefalin	US10793596B2	11-12-2027	DS + DP	Cara Therapeutics, Inc., Stamford, CT (US)	Synthetic peptide amides	[137]
Leuprolide acetate	US8921326B2	02-05-2031	DP	Takeda Pharmaceutical Co Ltd, Osaka (JP)	Sustained-release composition and method for producing the same	[105]
Rezafungin	US8722619B2	03-02-2032	DS + DP	Seachaid Pharmaceuticals, Inc., Durham, NC (US)	Antifungal agents and uses thereof	[138]

DS: Drug substance, DP: Drug product.

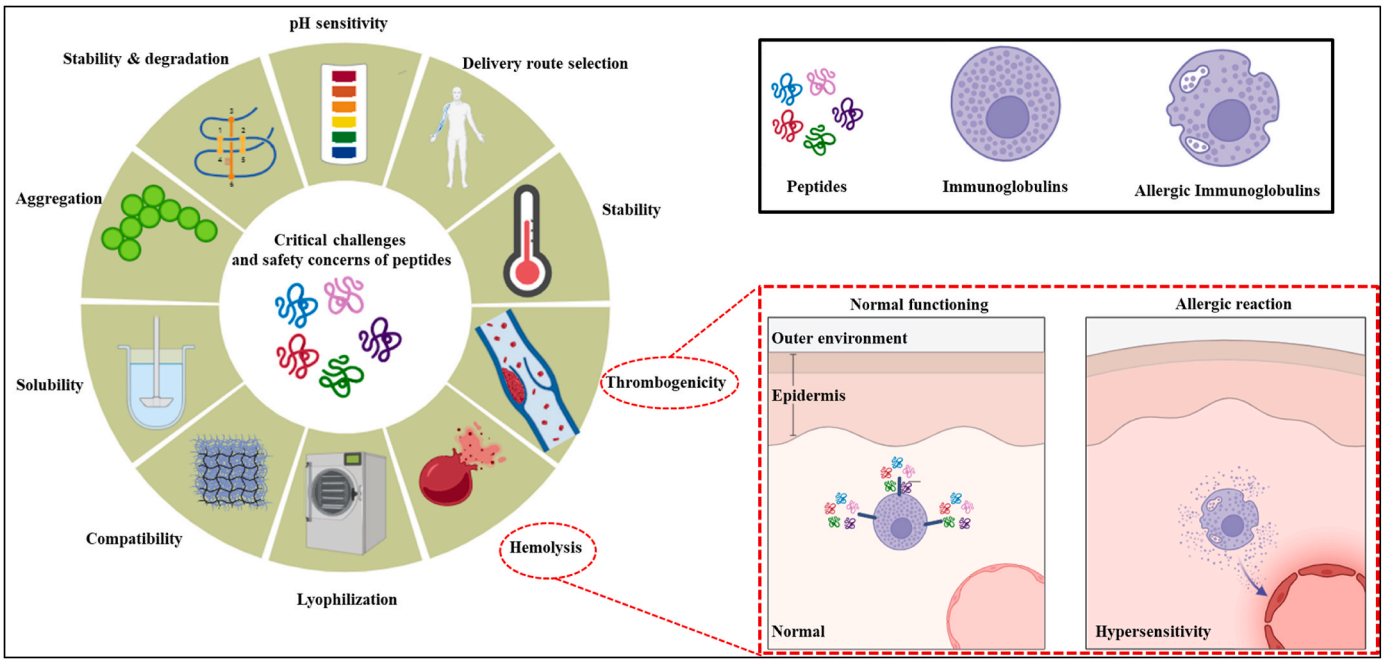

Fig. 2. Critical challenges of parenteral peptide formulation and safety concerns of excipients used in parenteral peptide formulation.

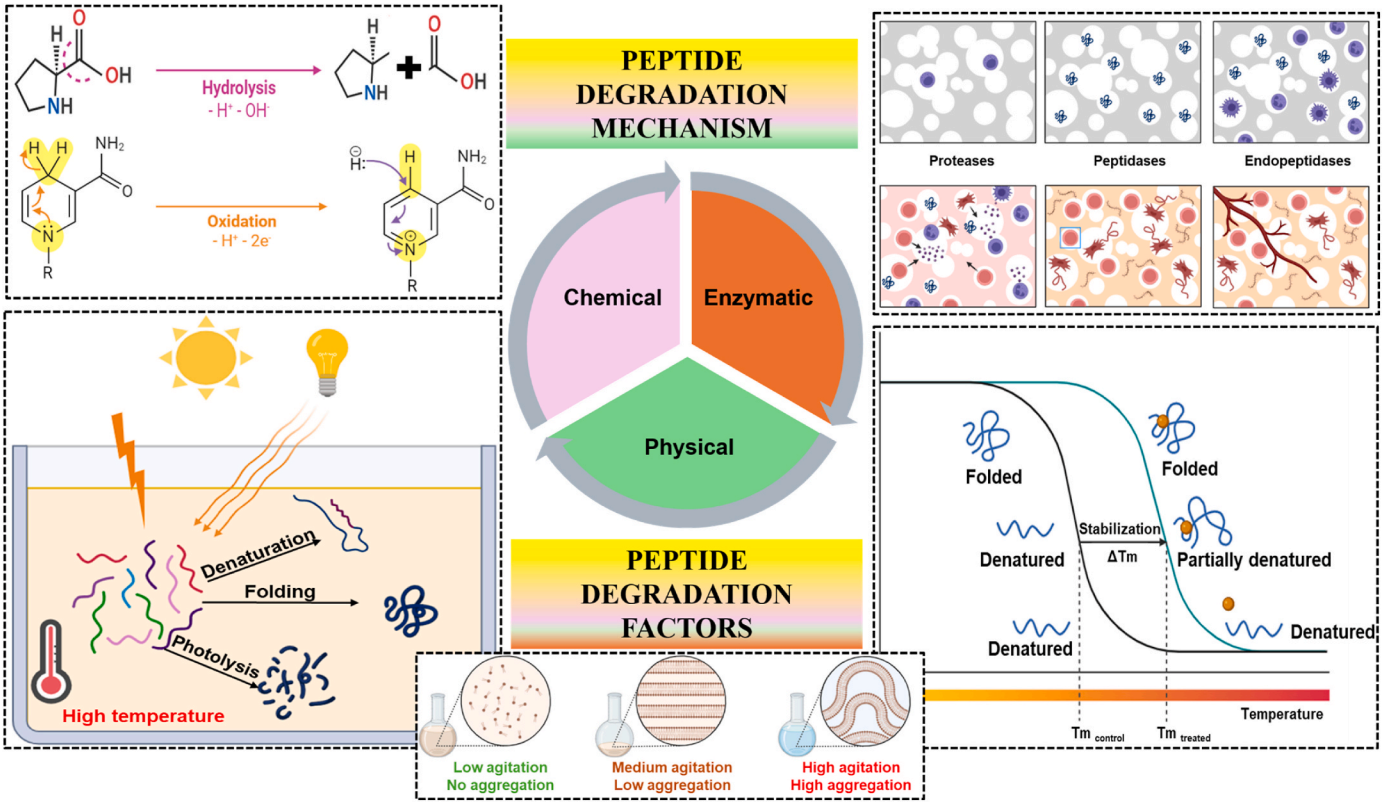

Fig. 3. Various mechanisms and responsible factors for peptide degradation/destabilization.

assessing the physicochemical environment within the lyophilized matrix presents significant challenges. Addressing this, Mingyue Li and collaborators pioneered the application of solid-state NMR techniques, utilizing histidine, a commonly employed buffer agent, as a molecular probe. Their groundbreaking research demonstrated the feasibility of studying microenvironmental acidity in lyophilized protein formulations. By analyzing histidine's chemical shift variations, the solid-state acidity within the lyophilized matrix could be quantified. Through comprehensive 13C and 15 N resonance assignments in both one- and two-dimensional NMR analyses, the protonation and tautomeric states of histidine lyophilized across a pH spectrum from 4.5 to 11.0 were elucidated. Remarkably, the study revealed a pH-dependent alteration in histidine's chemical profile in its amorphous state, shedding light on the intricate dynamics of lyophilized formulations [166].

Moreover, GlucaGen® (Glucagon) stands as the solitary approved peptide designated for the management of hypoglycemia. Nevertheless, it swiftly undergoes fibrillation upon exposure to the acidic pH requisite for solubility. While initially soluble at a pH of 3 or below, glucagon progressively coalesces to form a gel after a few hours. This gel predominantly comprises β-sheets or fibril structures, posing a potential risk of obstructing the narrow tubing of an infusion set. Consequently, glucagon is manufactured as a lyophilized powder and necessitates reconstitution in a provided diluent immediately prior to use [167]. Examples of commercially available lyophilized peptide formulations encompass TERLIVAZ® (Terlipressin) [70] SIGNIFOR® LAR [64], GATTEX® [69], TERLIVAZ® [70], ERAXIS™ [77], Caspofungin acetate for injection [79], COSMEGEN® [91], KIMYRSA™ [94], REZZAYO™ [28].

3.11. Compatibility with excipients

Compatibility with excipients is a critical consideration in the formulation of parenteral peptides and other pharmaceuticals. Ensuring that the excipients used in a parenteral peptide formulation are compatible with the peptide is essential to maintain the drug's efficacy and safety. The choice of excipients (e.g. diluents, stabilizers, preservatives, buffers, co-solvents, surfactants, and tonicity-adjusting agents) depends on the specific formulation requirements and the properties of the peptide. The choice of buffer is crucial as it affects the peptide's stability and solubility. Incompatible buffers can lead to pH-related degradation or precipitation. A peptide that requires an acidic pH range for stability may be incompatible with a phosphate buffer that maintains a higher pH. Some preservatives, while necessary to prevent microbial growth in multi-dose vials, may interact with the peptide, leading to instability or aggregation. The interaction between benzyl alcohol and certain peptides can result in aggregation or degradation [168]. Surfactants are used to improve solubility and prevent aggregation, but some peptides may be sensitive to specific surfactants [169]. Some strategies used for ensuring compatibility include excipient screening, optimization of screened excipients, and selection of a proper buffering system.

3.12. Delivery route selection

Selecting the appropriate delivery route for parenteral administration (e.g., SC, IM, and IV) of peptides is a crucial decision in its product development. The choice of route can significantly impact the efficacy, safety, and patient experience. The selection of the delivery route for a specific peptide is influenced by various factors, including the peptide's physicochemical properties, therapeutic indication, desired pharmacokinetics, and patient preferences [147]. Here are some general rules and considerations for selecting drug delivery routes.

- **Drug Properties**: The physicochemical properties of the drug, such as solubility, stability, and molecular weight, influence the choice of delivery route. For instance, highly water-soluble drugs may be suitable for intravenous administration, while poorly soluble drugs might require alternative routes or formulation strategies.
- **Desired Pharmacokinetics**: The desired onset of action, duration of effect, and systemic exposure profile help determine the appropriate route of administration. For rapid onset, intravenous or inhalation routes may be preferred, while sustained release formulations may be appropriate for prolonged action.
- **Patient Factors**: Patient characteristics such as age, disease state, comorbidities, and ability to tolerate certain routes of administration play a significant role. For example, pediatric or geriatric patients may have limitations with swallowing tablets or capsules, making liquid formulations or alternative routes more suitable.
- **Target Site**: The site of action or the intended target tissue can guide the selection of the delivery route. For localized therapy, topical, transdermal, or intra-articular routes may be appropriate, while systemic effects may require oral, parenteral, or inhalation administration.
- **Patient Acceptance and Compliance**: Patient preferences, convenience, and compliance with the chosen route of administration are crucial for treatment success. Selecting a route that aligns with patient preferences and lifestyle can improve adherence to the prescribed regimen.
- **Safety and Tolerability**: Considerations regarding the safety and tolerability of the selected route are paramount. Routes associated with lower risk of adverse effects or complications should be prioritized whenever possible.
- **Formulation Considerations**: The availability of suitable formulations and delivery devices for the chosen route should be taken into account. Factors such as stability, ease of preparation, and shelf-life of formulations are important considerations.

Overall, selecting the most appropriate drug delivery route involves a comprehensive assessment of multiple factors to optimize therapeutic outcomes while ensuring safety, efficacy, and patient acceptance. Collaboration between healthcare providers, pharmacists, and patients is essential in making informed decisions regarding drug delivery route selection. Additionally, regulatory agencies may have specific requirements for the route of administration based on safety and efficacy considerations. SC injection is commonly used for peptides like insulin because it allows for slower absorption and sustained release of the drug. The SC tissue has a rich blood supply, which facilitates absorption into the bloodstream. For Insulin delivery, SC route mimics its release from pancreas. IM injection is suitable for peptides that require rapid absorption but have a slower release profile than intravenous administration. Somatropin (recombinant human growth hormone) is often administered intramuscularly because it allows for gradual absorption over time. IV injection or infusion is used for peptides that require rapid and precise control of drug levels in the bloodstream [170]. Vasopressin (arginine vasopressin), which is used to manage conditions like diabetes insipidus and septic shock, is administered via IV to achieve rapid effects.

4. Strategies to overcome challenges of parenteral peptide formulation

Pharmaceutical industries employ various strategies to overcome these challenges. Here we have described some of these strategies including designing of prodrugs, structural modifications, development of nano and lipid based formulations, peptidomimetics and co-administration with enzyme inhibitors.

4.1. Prodrug design

Peptide prodrug design involves modifying the structure of a peptide to create a prodrug that undergoes chemical or enzymatic transformation *in vivo*, leading to the release of the active peptide. This approach aims to address challenges associated with the poor bioavailability, stability, or delivery of the native peptide. Enalapril is a prodrug that undergoes hydrolysis *in vivo* to form the active peptide enalaprilat and improves stability and bioavailability [171]. Fosaprepitant is the water-soluble prodrug of aprepitant, an antiemetic used in chemotherapy. Fosaprepitant is converted into the active form after intravenous administration through enzymatic hydrolysis [172].

4.2. Protective modifications

Protective modifications in parenteral peptides involve chemical alterations to enhance stability, bioavailability, and resistance to enzymatic degradation. These modifications can improve the overall pharmacokinetic profile of peptides administered via parenteral routes.

Desmopressin, a vasopressin analog, incorporates D-amino acids to improve stability. Substituting L-amino acids with their D-enantiomers can enhance peptide stability against enzymatic degradation, as enzymes typically recognize and cleave L-amino acids [173]. Cyclization of peptides through disulfide bridges or other chemical bonds can confer resistance to enzymatic degradation. Octreotide, a somatostatin analog, features cyclic structures to improve stability [174]. Peptoids are peptide mimetics where the side chains are attached to the nitrogen instead of the α-carbon. Semaglutide, a GLP-1 analog, incorporates peptoid modifications for increased stability and extended duration of action [175]. Other modification including *N*- methylation (e.g. leuprolide), Pegylation (e.g. pegfilgrastim), Acylation (e.g. exenatide).

4.3. Nanoparticle and lipid-based formulations

Parenteral administration of peptides often faces challenges related to their stability and pharmacokinetics. Nanoparticle and lipid-based formulations have been employed to overcome these challenges and improve the delivery of peptides. Exenatide (Bydureon) is a GLP-receptor agonist used for diabetes management available as sustained-release formulation utilizing polymeric microspheres that provide controlled release and reducing the dosage frequency of injections [176]. Sandostatin LAR is a long-acting release formulation using microsphere technology to prolong the release of octreotide, allowing for less frequent dosing. Insulin Glargine (Lantus) is formulated with microprecipitates in a slightly acidic solution, resulting in a prolonged and steady release of insulin over an extended period. It contains zinc, m-cresol, glycerol, polysorbate 20, and water for injection as inactive ingredients [177].

4.4. Peptidomimetics

Peptidomimetics are molecules designed to mimic the structure and function of peptides while overcoming some of their limitations, such as enzymatic degradation and poor oral bioavailability. When considering parenteral administration peptidomimetics become particularly interesting due to their potential to improve stability and therapeutic efficacy. Liraglutide (Victoza) is a peptidomimetic of native GLP-1, has been modified to resist degradation by dipeptidyl peptidase-4 (DPP-4) and has a prolonged half-life, making it suitable for once-daily SC injection [178]. Teriparatide (Forteo®) is a peptidomimetic form of PTH, administered SC and has been modified for increased stability and prolonged biological activity.

4.5. Co-administration with enzyme inhibitors

Co-administration of parenteral peptides with enzyme inhibitors is a strategy aimed at enhancing the stability and bioavailability of the peptides by inhibiting enzymatic degradation. Saquinavir and Nelfinavir is a protease inhibitor used in the treatment of HIV/AIDS. It is susceptible to rapid metabolism by cytochrome P450 enzymes in the liver and gastrointestinal tract. Ritonavir, another protease inhibitor used in HIV treatment, is co-administered with saquinavir. Ritonavir acts as a potent inhibitor of cytochrome P450 enzymes, particularly CYP3A4, slowing down the metabolism of saquinavir. This co-administration enhances the bioavailability of Saquinavir and Nelfinavir, allowing for more effective therapeutic outcomes [179]. When ritonavir and cyclosporine are co-administered, ritonavir inhibits the activity of CYP3A4, leading to elevated plasma concentrations of cyclosporine. Additionally, ritonavir serves as both an antiviral agent and a pharmacokinetic enhancer. In the management of type 2 diabetes, a combination therapy approach often involves the use of peptide hormones such as glucagon-like peptide-1 (GLP-1) analogues (e.g., exenatide, liraglutide) along with DPP-4 inhibitors like sitagliptin and saxagliptin. By inhibiting dipeptidyl peptidase-4 (DPP-4), these inhibitors prolong the half-life of endogenous GLP-1 and externally administered GLP-1 analogues [180]. For cancer immunotherapy utilizing peptide medications such as interleukin-2 (IL-2), adjunct administration of bestatin, an aminopeptidase inhibitor, is common practice. Aminopeptidase inhibitors work by extending the half-life of peptide medications, thereby enhancing their therapeutic efficacy through inhibition of enzymatic degradation [181]. In a recent study by Surve DH *et al.*, long-acting polymer-lipid hybrid nanoparticles (PLN) loaded with efavirenz (Efa) and enfuvirtide (Enf) were developed. These nanoparticles exhibited improved intracellular delivery to target T-cells and macrophages, crucial for combating the human immunodeficiency virus. Efa and Enf, both important in HIV therapy, were encapsulated within the PLN. Characterization studies revealed trehalose-induced spherical morphology, drug amorphization, and lack of drug-excipient interactions in lyophilized Efa-Enf Co-loaded PLN. In vitro release experiments demonstrated sustained drug release profiles from the PLN. Cytotoxicity assays conducted on Jurkat E6.1 T-cells and U937 macrophage cells showed minimal adverse effects, with modest hemolytic, platelet, and leukocyte aggregation. Circular dichroism spectra confirmed the presence of an α-helix conformation of Enf post-encapsulation. Biodistribution studies using near-infrared dye--loaded PLN as a surrogate for Efa-Enf PLN revealed non-uniform distribution within 2 h post-intravenous injection, with notable accumulation in various organs including the spleen, liver, lymph nodes, and brain. Subcutaneous administration led to sustained release from the injection site depot, resulting in prolonged presence in reservoir sites such as the brain, liver, spleen, lymph nodes, and female reproductive tract over a five-day period [182].

5. Excipients used in parenteral peptide formulation: safety concerns

Excipients are non-active substances included in a formulation to aid in various aspects of drug delivery, stability, and safety. However, it is crucial to consider their safety, especially in parenteral formulations, where they come into direct contact with the bloodstream. Some excipients may trigger allergic reactions in certain individuals, including hypersensitivity reactions like skin rashes, itching, or more severe anaphylactic reactions. Common allergenic excipients include preservatives like benzyl alcohol or certain stabilizers [183]. Excipients can sometimes induce an immune reaction in the body, leading to the formation of antibodies that can reduce the efficacy of the peptide or lead to immune-related side effects. Polysorbate 80, a common solubilizing agent, has been associated with immunogenicity concerns [184]. Excipients may have inherent toxicity or can become toxic when administered at higher concentrations. The kidneys and liver are primarily responsible for metabolizing and excreting these excipients. High levels of exposure can lead to organ damage or dysfunction [185]. The compatibility of excipients with the peptide and the overall formulation is crucial. Incompatibility can lead to aggregation, precipitation, or degradation of the peptide, which can reduce efficacy and pose safety risks [41]. Sometimes, excipients added to provide long-term stability to the peptide formulation cause degradation of the peptide over time, leading to a decrease in its efficacy or the development of potentially harmful degradation impurities/products.

Excipients can cause irritation or inflammation at the injection site. This can range from mild discomfort to more severe reactions, including abscess formation or tissue damage [186]. Excipients like surfactants or particulate matter can contribute to thrombogenicity concerns. Surfactants are commonly used excipients in various pharmaceutical formulations, including intravenous (IV) formulations, oral tablets, and topical preparations. While surfactants are generally considered safe when used within recommended concentrations, there have been instances where certain surfactants have been associated with thrombogenicity, particularly when administered intravenously. Some surfactants may raise thrombogenicity concerns for example in drug formulations, polysorbate 80 has been implicated in a number of systemic reactions (e.g., hypersensitivity, nonallergic anaphylaxis, rash) and injection- and

infusion-site adverse events (ISAEs; e.g., pain, erythema, thrombophlebitis). Polysorbate 80 has also been implicated in cases of renal and liver toxicity [187].

Excipients in parenteral formulations can interact with blood components, potentially leading to hemolysis [188]. Particulate contamination, such as visible or subvisible particles in the formulation, can be a safety concern and may cause embolisms or other adverse reactions when injected. Manufacturers must implement strict quality control measures to minimize the presence of particles in formulations [189]. Residual solvents used during manufacturing processes can remain in the final product. These solvents may be toxic and pose safety risks if not adequately removed. To mitigate these safety concerns, pharmaceutical companies conduct rigorous safety assessments of excipients used in parenteral peptide formulations. This includes extensive *in vitro* and *in vivo* studies to assess their compatibility with the peptide and their impact on patient safety. Regulatory agencies provide guidelines and requirements for safety evaluation of excipients in parenteral formulations. Researchers and manufacturers must adhere to these guidelines to confirm the safety and efficacy of peptide-based parenteral products.

6. Peptide-excipient interactions in parenteral formulations

The peptide molecule's interaction with the excipients is critical for designing parenteral peptide formulations. Excipient responses depend on formulation process design, including chemical type, peptide-to-excipient ratio, moisture, microenvironmental pH, temperature, and light. In assessing drug product unknown contaminants, functional group incompatibilities must be considered [190]. As peptides are composed of amino acids, they are very prone to degrade easily, compromising their efficiency and safety [139]. Excipient-peptide interaction requires knowledge of excipient chemistry and careful selection. The interaction might be physical (adsorption, complexation, viscosity), chemical (hydrolysis, isomerization, oxidation, polymerization, and Maillard reactions), or biopharmaceutical.

Oxidation is one of the dominant problems that affects parenteral peptide formulation safety and effectiveness following sealing in vials, ampoules, syringes, bags, or another administration method. Methionine, cysteine, histidine, tryptophan, and tyrosine are oxidized often [191]. Additionally, the dissolved oxygen in parenteral formulations and the void volume of the container containing oxygen may cause oxidation. To avoid those formulations scientists should use strategies that include a selection of containers that have an internal coating, which absorbs the oxygen, and use nitrogen purging during manufacturing, filling, and sealing. Due to oxidation, benzyl alcohol forms benzaldehyde dibenzyl acetal and affects the peptide stability and efficacy [192]. Recently, Mingyue Li *et al.* (2022) studied the interaction of benzyl alcohol and m-cresol with acyl-peptide A. The authors reported that there was no observed chemical shift perturbation with benzyl alcohol, indicating the absence of interaction and aggregation. Whereas, after the addition of m-cresol (1% w/v) to the peptide with incubation of 24 h, it resulted in 25 % w/w of acyl-peptide A insoluble aggregates [193].

Additionally, certain products could be isomerization-prone. When TRIS buffer is used in a peptide formulation and kept at 70 °C, formaldehyde is released through degradation [194]. It has been shown that after autoclaving, dextrose in fructose produces 5-hydroxymethyl furfuraldehyde [195]. This impurity may produce a Schiff base and provide the illusion of color by reacting with a primary amino group. Primary amines may undergo a Maillard reaction with glycosidic hydroxyl groups like those in dextrose [196].

7. Excipient-packaging interactions

Parenteral formulators must examine the main packing components since excipients may interact with them despite their apparent inertness. Glass and plastic are common primary packaging materials in parenteral formulations [197]. To prevent leakage from the used container closure system (CCS), which includes vials, syringes, ampules, stoppers, and caps, as well as the adsorption of excipients and active pharmaceutical ingredients (APIs), the packaging material used must be compatible with the formulation. Glass containers can interact with the formulation components and promote leaching from the presence of various oxides, such as boron, calcium, iron, magnesium, and potassium. Glass is composed of cations of iron and manganese oxide, which can stimulate oxidation and result in degradation of the formulation [198]. Moreover, silicone oil serves as a common lubricant in glass syringes and cartridges, mitigating friction between the inner surface of the glass barrel and the elastomeric plunger stopper. However, its presence can lead to the appearance of intrinsic, non-proteinaceous particles within the formulation upon migration. Consequently, extensive research has been conducted to investigate the adverse effects of these emulsion droplets on the development and commercialization of biotherapeutics. Molecular interactions and interfacial pressures induced by silicone oil particles have been identified as potential causes of protein aggregation [199]. Despite these concerns, the impact of syringe age on silicone oil migration from the siliconized layer into the drug product remains poorly understood. A recent study by J. Song et al. aimed to address this gap by comparing the extrusion force and subvisible particle count of siliconized syringes from two different manufacturers. These syringes were stored at room temperature for two to three months (for fresh syringes) and for thirteen to fourteen months (for aged syringes) before being filled and subsequently kept at 40 °C for an additional three months. The study's findings revealed significant differences between fresh and aged syringes. Fresh syringes exhibited a subvisible particle count 2.5 times higher than that of aged syringes, along with a doubling in extrusion force. These results suggest that the storage period of glass syringes before filling directly impacts the extent and quantity of silicone oil migration. This observation underscores the importance of considering syringe storage time during the development phase [200].

Tocopherols may be absorbed into hydrophobic plastic containers and impact the stability of formulation. Rubber is an essential part of caps that may have unfavourable interactions with certain preservatives used in formulations [201]. Furthermore, from rubber stoppers, zinc and other leachables may leach out and can cause the oxidation of peptides [202]. To avoid these incidences, formulation scientists should thoroughly conduct compatibility studies with CCS.

In summary, parenteral excipient-packaging interactions are crucial to pharmaceutical development. Understanding and mitigating these interactions to ensure product safety, effectiveness, and stability during shelf life is prime important. This requires extensive compatibility research and regulatory compliance.

8. Characterization of peptide: analytical perspective

Peptide and protein medications undergo comprehensive analysis employing various sophisticated analytical methodologies. These methods can be categorized as follows. (a) Performance of quality control techniques (high-performance liquid chromatography and mass spectroscopy). (b) Spectroscopy, including nuclear magnetic resonance, fluorescence, circular and linear dichroism, Raman, and Fourier transform infrared spectroscopy. (c) Microscopy, including optical and polarized light microscopy, atomic force microscopy, and scanning and transmission electron microscopy. (d) Scattering (X-ray diffraction, small angle X-ray and neutron scattering), and (e) Rheological characterisation of bulk materials (mostly hydrogels). The quality control test outlining the methods required to clarify the purity of the peptide and validate its molecular structure. One significant and growing class of medicines are synthetic peptides. Synthetic peptides, although smaller in size than monoclonal antibodies and other proteins, are prone to a variety of intricate structural alterations that stem from the raw ingredients, production method, and storage circumstances. The utilization of liquid chromatography–mass spectrometry and its challenges,

solutions, pitfalls, and future perspectives for peptide characterisation were recently highlighted in a review paper [203].

Subsequently, the spectroscopic techniques that pinpoint the precise secondary structure of peptide-based nanomaterials allow for the discovery of the primary self-assembly elements that propel the peptides into distinct structures and nanomaterials [204]. Phyo et al. using NMR spectroscopy recently revealed the molecular processes of biologics drug transport and stability. The molecular mechanisms underlying protein stability in parental and solid-state formulations, the structural underpinnings of membrane affinity and translocation of peptides and proteins as represented by CPPs, and the potential application of cutting-edge NMR techniques to investigate in-situ drug delivery and biologic stability have all been elaborated. In addition to seeing peptide structures, the current microscopy techniques can assist in identifying structural characteristics, time-dependent events, and additional attributes that are crucial for applications [205]. This will be further enhanced by the application of scattering techniques, such as wide-angle X-ray scattering and small angle scattering, to characterize peptide-based nanomaterials over a range of length scales, from atomic spacing to larger (~500 nm) structures [206]. Finally yet importantly, peptide-based hydrogels are characterized using techniques including mechanical and rheological testing [207].

9. Future perspective and conclusion

The future perspective of excipients used in parenteral peptide formulations is likely to be shaped by several key factors, including advances in pharmaceutical technology, regulatory requirements, and the evolving landscape of drug delivery. Peptides are inherently less stable than small molecules, making formulation and stabilization crucial. Future excipients may focus on enhancing peptide stability during storage and administration. This could involve the development of novel excipients or modifications to existing ones to protect peptides from degradation. Precision medicine is a growing trend in healthcare. Excipients may be tailored to enable peptides targeted delivery to specific tissues or cells, improving the therapeutic index and reducing off-target effects. Excipient research may center on improving the bioavailability of peptides, potentially through the development of excipients that enhance absorption, permeability, or cellular uptake. Safety remains a paramount concern in parenteral drug formulations. Future excipients should be rigorously tested for biocompatibility and safety. Excipient selection may shift towards more biodegradable materials that are less likely to cause adverse reactions.

Regulatory agencies, such as the FDA and EMA, are continually updating guidelines for parenteral drug products. Excipient manufacturers and pharmaceutical companies will need to stay current with these regulations to ensure compliance. As the field of personalized medicine advances, there may be a demand for customized excipients that can be tailored to the unique needs of individual patients or patient populations. This could involve 3D printing of drug delivery systems or formulations. Sustainability concerns are increasingly influencing pharmaceutical development. Future excipients need to be sourced and manufactured with environmental sustainability in mind, with an emphasis on reducing waste and minimizing the environmental impact of drug production. While innovation is essential, cost-effectiveness will remain a key consideration. Excipients should not only improve drug performance but also be economically viable for large-scale production. Excipient research may focus on compatibility of peptides with other active pharmaceutical ingredients and optimizing their combination therapies. The development of advanced analytical techniques will enable better characterization and understanding of the interactions between peptides and excipients.

To summarize, this article explores the essential domain of excipients employed in parenteral peptide formulations, emphasizing their crucial contribution to shaping the current landscape of peptide pharmaceuticals. The approval by the FDA of parenteral peptide formulations highlights the increasing importance of these medicines in the field of clinical practice, emphasizing their efficacy in the treatment of diverse disorders despite their possessing some key limitations, such as stability, degradation, and aggregation. Furthermore, it is crucial to prioritize the safety of the excipients used in these formulations, necessitating a comprehensive evaluation and strict adherence to rigorous safety protocols. The comprehension of the interaction between certain excipients and packaging materials is crucial for ensuring the safety and effectiveness of peptide formulations. Regulatory concerns are of utmost importance in shaping the progress and authorization of these formulations, hence requiring diligent adherence to the ever-evolving requirements. The potential of parenteral peptide formulations in addressing these complexities is promising, as ongoing progress in excipient technology is expected to facilitate novel approaches for efficient and secure drug administration.

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