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Application of Peptides in Pharmaceutical Industry

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Abstract:

Peptides have emerged as versatile entities in the pharmaceutical industry by playing pivotal roles in drug discovery, development, and targeted drug delivery systems. While, the US Food and Drug Administration (FDA) has approved 60 peptides, and more will soon be available for purchase. In this review we provide a brief overview of the multifaceted applications of peptides, highlighting their significance in pharmaceutical research and therapeutics. Peptides a small molecule that consist of desirable biocompatibility and biodegradability. The growing importance of peptides as drug candidates for the treatment of diabetes, obesity, Crohn's disease, osteoporosis, cancer, cardiovascular disease, immunotherapy, acromegaly, enuresis, pain, and antimicrobials with a focus on their advantages, such as high specificity and reduced toxicity. Nevertheless, the critical role of peptides in the development of targeted drug delivery systems, design strategies, interactions with receptors, and their impact on drug efficacy and safety is to draw attention. As peptides continue to redefine the landscape of pharmaceuticals, this abstract provides a concise view of their current state and outlines the promising future they herald for precision medicine and innovative therapeutic interventions.

Keywords: Peptides, Pharmaceutical Industry, Targeted- Drug, Drug-delivery

Introduction:

Peptides have emerged as promising candidates in the pharmaceutical industry. The crucial role of peptides in targeted drug delivery systems has offered numerous applications. With the emergence of peptides as a versatile molecule in drug development, the pharmaceutical industry has witnessed a transformative shift in recent years. Multifaceted applications of peptides include treatment of diabetes, obesity, Crohn's disease, osteoporosis, cancer, cardiovascular disease, immunotherapy, acromegaly, enuresis, pain, and microbial diseases (Stevenson, 2009).

With inherent issues such as limited specificity, off-target effects, and systemic toxicity, targeted drug delivery is still a challenging task. Pharmaceutical drugs are classified into two categories: conventional "small molecule" drugs, which usually have molecular weights less than 500 da, and the bigger "biologics," which usually have molecular weights greater than 5000 da. Conventional small-molecule drugs may have poor target selectivity because of their small size, which frequently results in side effects. In contrast, peptide based therapeutics have more selective interactions with their targets, which makes them extremely specific. However, poor membrane permeability, low bioavailability, and metabolic instability have hindered their wider applications in the pharmaceutical industry (Craik, Fairlie, Liras, & Price, 2013). Currently, the US Food and Drug Administration (FDA) has approved 60 peptide drugs (Negahdaripour et al., 2019), while more than 600 are in clinical and preclinical trials (Erak, Bellmann-Sickert, Els-Heindl, & Beck-Sickinger, 2018).

Peptides are short chains of amino acids, the building blocks of proteins, and their biological significance extends beyond structural and regulatory functions (Sánchez & Vázquez, 2017). The pharmaceutical industry has already recognized the potential of peptides, as alternative therapeutic as well

as vehicles for targeted drug delivery. Peptides have so far developed into significant endogenous hormones, growth factors, neurotransmitters, signaling molecules, immune system and defense agents, and more after being precisely engineered to interact with biological targets (Craik et al., 2013). The overall status of peptides as potential alternatives in the pharmaceutical industry is summarized in Table 1.

Table 01- Advantages and disadvantages of peptides as drugs

Advantages	**Disadvantages**
High potency	Poor metabolic stability
High Selectivity	Poor membrane permeability
A broad range of targets	Poor oral bioavailability
Potentially lower toxicity than small molecules	High production coasts
Low accumulations and biological diversity	Rapid clearance
Discoverable size at peptide level size	Limited poor solubility in certain instances

One of the defining features of peptides is their structural diversity and functional adaptability. The amino acid sequence of a peptide determines its unique three-dimensional structure and, consequently, its interactions with biological targets. This versatility allows for the design of peptides with specific binding affinities to target cells, tissues, or receptors, forming the basis for their application in targeted drug delivery systems (Greer, Erickson, Baldwin, & Varney, 1994). Peptides offer a wide array of targeting options. They may be made to identify and attach to overexpressed receptors on sick cells, setting them apart from healthy ones. The foundation of targeted medication delivery is this innate selectivity, which tries to spare unaffected tissues while delivering therapeutic chemicals exactly where they are necessary. This strategy has a lot of potential to improve the medication therapeutic index and lower side effects(Cahill, 2010). The majority of peptide modification techniques have been designed to replace or selectively alter amino acids with groups that are not naturally present in peptides. Modified peptides by using a variety of synthetic amino acids with distinct functions can be done using synthetic organic chemistry. Biomolecules (lipids, various amino acid sequences, steroids, etc.) and synthetic molecules (polyethylene glycol, or PEG units, artificial amino acids for introducing modifications like disulfide bond mimetics or stapled peptides, etc.) are two types of molecules that are frequently conjugated with peptides(Erak et al., 2018).

Due to their inherent biological properties and diverse structures Peptides have gained attention as potential carriers for targeted drug delivery. Various studies have demonstrated the effectiveness of peptide-based vehicles in delivering therapeutic agents to specific cells or tissues. Examples include peptides designed to target cancer cells, inflammatory sites, or specific receptors, thus minimizing off-target effects(Accardo, Aloj, Aurilio, Morelli, & Tesauro, 2014).

This article aims to explore the recent advancements and applications of peptide therapeutics in enhancing precision and efficacy within drug delivery processes.

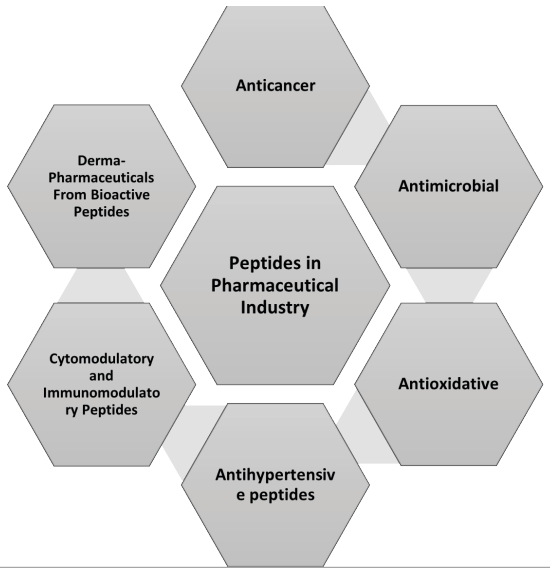

Figure 1: Overview of Peptides in Pharmaceutical Industry

Biologically active peptides can be produced by a variety of methods, including whole extraction, bottom-up construction, whole expression, and up-down degradation. Currently, the therapeutic potential of bioactive peptides is harnessed in various forms of pharmaceutical applications due to their high degree

of specificity, broad therapeutic activity, and low biodeposition in bodily tissues (Danquah & Agyei, 2012).

Mode of Action of Pharmaceutical Peptides:

The mode of action of therapeutic peptides is diverse. Peptides exhibit a similar form of broad-spectrum defense activity against bacteria, fungi, viruses, and some parasites(Talapko et al., 2022). However, in certain immunomodulatory and anticancer activities, the underline host defense mechanism of the peptide is uncertain.

The mechanisms by which Antimicrobial Peptides (AMPs) exert their antimicrobial effects are multifaceted and can be categorized into several key modes of action such as (1) Disruption of Cell Membrane Integrity: Considered the primary mechanism of action for many AMPs is the disruption of microbial cell membranes. Disrupting the both hydrophobic and hydrophilic regions of the cell membrane disrupts the membrane integrity by forming pores or channels. This leads to increased permeability, loss of ion gradients, leakage of cellular contents, and ultimately cell death (2) Binding to Intracellular Targets: While several AMPs can penetrate microbial cells and target intracellular components, such as DNA, RNA, proteins, or enzymes; while interfering with vital cellular processes, disrupt the synthesis of essential macromolecules, or inhibit crucial enzymatic activities, ultimately leading to microbial death and (3) Immune Modulation: AMPS may stimulate immune cells, such as macrophages and neutrophils, to enhance phagocytosis and the release of inflammatory mediators(Haney, Mansour, & Hancock, 2017; Luo & Song, 2021). AMPs can also contribute to wound healing and tissue repair. Other forms of the mode of mechanism include Anti-Biofilm Activity and Selective Targeting of Microbes which work by preventing the formation of biofilms or disrupting pre-existing biofilms and selectively target microbes while sparing host cells respectively (Raheem & Straus, 2019).

Applications of Peptides in Pharmaceutical:

The treatment of diabetes, osteoporosis, cancer, gastrointestinal disorders, cardiovascular disease, immunosuppression, acromegaly, enuresis, and antiviral, antibacterial, and antifungal indications is greatly aided by therapeutic peptides (Table 02). Nevertheless, the delivery patterns of many pharmaceuticals derived from biotechnology are not optimal. The production of novel peptidomimetics with enhanced stability and permeability can enhance the therapeutic profile. Additionally, drug delivery provides a means of enhancing the efficacy and distribution profile of an established peptide, creating new indications, extending the product's shelf life when patents expire, enhancing patient quality of life, and maintaining competitiveness against generic rivals.

Table 02- Examples of Therapeutic peptides and sequences (Stevenson, 2009)

Therapeutic usage	Bioactive peptide	Sequences
Anti-diabetic	Glucagon	His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-Lys-Arg
	Pramlinitide	Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NHE
	Exenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-LysAsn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2
Anticancer	Histrelin	pGlu-His-Trp-Ser-Tyr-N-benzyl-D-His-Leu-Arg-Pro-NH_2
	Leuprorelin	pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NH_2

Immunomodulatory	Cyclosporin	Cyclic MeBmt-Abu-Sar-MeLeu-Val-MeLeu-Ala-D-Ala-MeLeu-MeLeu-MeVal
	MPB8298	Asp-Glu-Asn-Pro-Val-Val-His-Phe-Phe-Lys-Asn-Ile-Val-Thr-Pro-Arg-Thr
Antiviral	Enfuvirtide	CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-GluLeu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp
	Thymalfasin	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-AlaGlu-Asn-OH
Antibacterial	Bacitracin	D-Orn*-Ile-D-Phe-His-D-Asp-Asn--Lys*-Ile-D-Glu-Leu, *disulfide bond (1-7)
	Colistin	Dbu-Thr-Dbu-Dbu*-Dbu-Leu-Leu-Dbu-Dbu-Thr*, * disulfide bond (4-10)
	Gramidicin	HCO-Val-Gly-Ala-(D-Leu)-Ala-(D-Val)-Val-(D-Val)-Trp-(D-Leu)-Trp-(D-Leu)-Trp-(D-Leu)-Trp-NHCH2CH2OH
Antifungal	Micafungin	1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L- ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine] pneumocandin A0
	Lactoferrin	Gly-Arg-Arg-Arg-Arg-Ser-Val-Gln-Trp-Cys-Ala
Cardiovascular	Nesiritide	Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-Cys*-Phe-Gly-Arg-Lys-Met-Asp-Arg-Ile-Ser-Ser-Ser-Ser-Gly-Leu-Gly-Cys*-Lys-Val-Leu-Arg-Arg-His-OH, *disulfide bond (10-26)
	Rotigaptide	Ac-D-Tyr-D-Pro-D-Hyp-L-Gly-D-Ala-L-Gly-NH2

Precision in Inflammatory Diseases:

Peptides are essential for targeted drug delivery of inflammatory illnesses. In conditions like rheumatoid arthritis and inflammatory bowel disease inflammation is a hallmark (Cader & Kaser, 2013). Peptides can be designed to target specific immune cells or inflammatory markers. Vasoactive intestinal peptide (VIP), a mediator with well-established anti-inflammatory and immunomodulatory properties, regulates every step in rheumatoid arthritis between the entry of pathogens and Th cell development. This "neuro-immuno-peptide" affects many cell subpopulations that are involved in rheumatoid arthritis, such as macrophages, fibroblast-like synoviocytes (FLS), and lymphocytes, by modifying their pathogenic activity. Furthermore, in FLS from rheumatoid arthritis patients, VIP reduces the expression of pattern recognition receptors (PRR), such as toll-like receptors (TLRs) (Villanueva-Romero et al., 2018). This targeted approach holds the promise of delivering anti-inflammatory agents directly to affected sites, improving therapeutic outcomes while minimizing systemic immunosuppression. Peptide-based drug delivery systems can leverage the overexpression of certain receptors on immune cells or inflamed tissues. The specific binding of peptides to these targets facilitates the selective delivery of anti-inflammatory drugs, presenting a viable strategy for managing chronic inflammatory conditions.

Tailoring Peptides for Infectious Diseases:

Due to the versatility of peptides, specific medication delivery methods for infectious disorders can be developed. Peptides can be engineered to identify distinct surface features or antigens on infections, so enabling the targeted administration of antimicrobial medicines(Pham, Loupias, Dassonville-Klimpt, &

Sonnet, 2019). This approach holds the potential to improve the efficacy of antibiotics while minimizing the risk of resistance development. The targeted delivery of antimicrobial peptides or conventional antibiotics using peptide carriers can enhance the concentration of the therapeutic agent at the site of infection. It has been shown that specialized targeted strategies can effectively combat major illnesses including malaria, HIV, and tuberculosis. Future opportunities are highlighted and an example of the use of tailored delivery in the treatment of veterinary illnesses is provided(Devarajan, Dawre, & Dutta, 2015). This targeted strategy may prove valuable in addressing challenging infections and preventing the widespread use of broad-spectrum antibiotics, contributing to the global effort to combat antimicrobial resistance.

Design Strategies for Peptide-Based Drug Delivery

The majority of peptide based pharmaceuticals are manufactured (Figure 02) with the help of new technological developments. In addition to these, the production of this new drug can also be done using both conventional and contemporary methods (Zompra, Galanis, Werbitzky, & Albericio, 2009) due to various economic and environmental concerns, particularly with large-scale production.

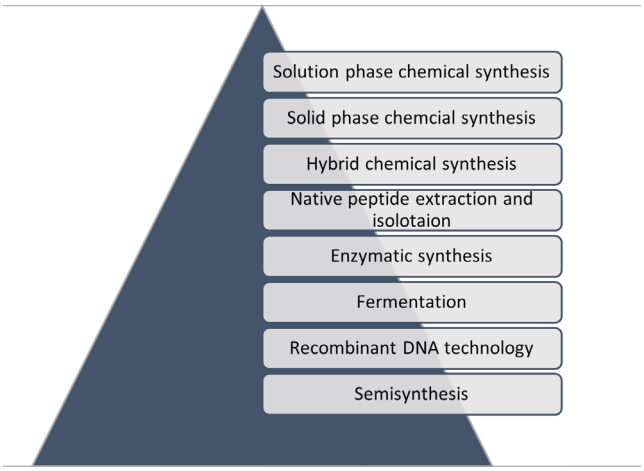

Figure 02- Manufacturing of peptides

The effectiveness of peptides as targeted drug delivery vehicles pivots on strategic design considerations. Researchers employ various approaches to optimize the properties of peptides for drug delivery applications. Rational design involves tailoring the peptide sequence to achieve specific physicochemical characteristics, such as stability, solubility, and membrane permeability(Hu et al., 2020).

Nanotechnology has become an enabling technology in the pharmaceutical industry. Therefore, incorporating nanotechnology into peptide-based drug delivery systems has emerged as a powerful strategy. Nanoparticles, liposomes, and micelles can encapsulate therapeutic agents, protecting them from degradation and facilitating controlled release(McClements, 2018). Peptide-nanoparticle conjugates offer enhanced pharmacokinetics and bioavailability, providing a versatile platform for targeted drug delivery. While examples of cyclic peptides typically stack into nanotubes, branching peptides frequently form micelles or vesicles, and linear peptides and their derivatives self-assemble into nanostructures such as nanofibers, nanoribbons, nanotubes, or vesicles(Mammadov, Tekinay, Dana, & Guler, 2012).

Peptides in Cancer Therapy:

Cancer therapy is one of the fields where peptides show the greatest promise as targeted medication delivery vehicles. Peptides can be designed with the ability to selectively recognize and bind to the overexpressed receptors on cancer cells. The recent study on peptide cytotoxicity was conducted on MDA-MB-231 and MCF-7 breast cancer cells to target cancer cells, the lytic peptide (KLAKLAK)2 is attached to either a gastrin-releasing peptide (GNHWAVGHLM) or a cancer-cell binding peptide (LTVSPWY) that is chosen from peptide libraries, while cancer cells ingested the fusion peptides, which caused the cell membrane to break and resulted in the cells dying quickly (Shadidi & Sioud, 2003). By targeting these specific receptors, peptide-drug conjugates can deliver therapeutic payloads directly to cancer cells, minimizing damage to surrounding tissues. The use of peptides in cancer-targeted drug delivery is exemplified by the development of peptide ligands for receptors like HER2 in breast cancer or integrins in various malignancies. The targeted approach not only enhances the efficacy of anticancer drugs but also reduces systemic exposure, mitigating adverse effects commonly associated with chemotherapy(Lesniak et al., 2009).

Overcoming Biological Barriers:

One of the remarkable features of peptides in drug delivery is their ability to overcome biological barriers that often impede the delivery of therapeutic agents. Peptides can traverse barriers such as the blood-brain barrier (BBB), enabling the targeted delivery of drugs to the central nervous system. This capability opens new avenues for treating neurological disorders and brain tumors(Spencer et al., 2020). The design of peptides with inherent properties to bypass or interact with biological barriers involves a deep understanding of the physiological and biochemical characteristics of these barriers. Peptide-based drug delivery systems that effectively navigate these challenges hold great promise for advancing treatment options for conditions affecting the brain and other hard-to-reach tissues. The majority of psychoactive medications cause the BBB to become more permeable, reducing the physical restriction of endothelial tight junctions and facilitating the large-scale passage of most therapeutic molecules via the BBB. Additionally, an excess of molecules floods the brain, leading to osmotic imbalances, a significant impact on membrane permeability, and a blockage or restriction of the usual flow of nutrients(Upadhyay, 2014).

The transition of peptide-based drug delivery from theoretical concepts to clinical applications is exemplified by several success stories. For instance, the FDA-approved drug Lupron Depot utilizes a peptide-based delivery system for the treatment of prostate cancer and endometriosis. The peptide carrier ensures a sustained release of the therapeutic agent, extending the duration of its therapeutic effects and improving patient compliance (Upadhyay, 2014).

Similarly, the success of targeted drug delivery using peptides is evident in the field of diabetes management. α-glucosidase and α-amylase inhibitors have been first-line treatments for type 2 diabetes since the 1990s. Inhibiting these digestive enzymes is thought to be an efficient way to lower blood sugar levels since they are involved in the breakdown of complex carbs into glucose. Inhibiting DPP IV and activating GLP-1 receptors with GLP-1 analogs and incretin mimetics is another often utilized therapeutic approach. Important incretin hormone GLP-1 stimulates insulin release, inhibits glucagon synthesis, and slows stomach emptying to assist in controlling blood glucose levels. Nevertheless, DPP IV quickly degrades and inactivates this endogenous hormone(Antony & Vijayan, 2021). Peptide-based formulations enable the targeted delivery of insulin or other antidiabetic agents, mimicking the physiological release of insulin in response to glucose levels. This targeted approach holds the potential to revolutionize diabetes treatment, offering improved glycemic control and reduced risk of hypoglycemia(Rekha & Sharma, 2013).

Challenges and Future Directions:

Despite the promising advancements, challenges persist in the widespread adoption of peptide-based drug delivery systems. The significant role of peptides in the pharmaceutical industry, specifically in the realm of targeted drug delivery systems is still developing. As research in this field continues to evolve, the integration of peptides into drug delivery strategies holds immense promise for advancing precision medicine. The safety and effectiveness of drugs are significantly affected by tailored drug delivery.

Peptides enhance treatment efficacy by precisely delivering therapeutic ingredients to the site of action. Lower therapeutic doses by reducing the possibility of systemic toxicity and side effects can be achieved using this focused strategy. Moreover, the capability of peptides to cross biological barriers such as the blood-brain barrier opens up new therapeutic avenues for diseases that were previously difficult to treat. In neurodegenerative illnesses, where getting therapeutic drugs to the brain is a major challenge. Peptide-based drug delivery systems show lots of promise in this regard.

Despite the potential benefits peptides have for targeted medication delivery, there are a few limitations to prevent their widespread applications including the immunogenicity, stability, and susceptibility to enzymatic breakdown. Peptides may cause an immune response in the body, leading to immunogenicity concerns. This immune response can potentially reduce the efficacy of peptide-based nanocarriers and may even cause adverse reactions. To ensure that peptide-based nanocarriers are well-tolerated inside the biological system, it is imperative to achieve

optimal biocompatibility. Research is still being done to develop new treatments, such as those that employ peptide modifications, nano conjugation techniques, and advanced delivery systems. Meanwhile, peptides are frequently vulnerable to enzymatic breakdown by bloodstream and tissue-resident proteases. This susceptibility can compromise the stability of peptide-based nanocarriers, leading to premature degradation and limiting their effectiveness. Strategies such as peptide modifications, cyclization, or the incorporation of non-natural amino acids aim to enhance stability. Nevertheless, it is still very difficult to precisely target sick cells or tissues while reducing off-target effects. Peptide-based nanocarrier design must provide high target specificity while taking individual differences in target expression and illness heterogeneity into account. To increase selectivity, targeted ligands must be incorporated or the peptide sequence must be optimized.

Predicting and optimizing peptide behavior is greatly aided by the incorporation of computational techniques, such as molecular modeling and simulations. These resources support the logical design of peptides with improved pharmacokinetic, stability, and selectivity. Future directions in the field of peptide-based drug delivery systems involve exploring synergies with emerging technologies. The intersection of peptides with gene therapy, personalized medicine, and precision medicine holds immense potential. Tailoring peptide carriers to individual patient profiles could further enhance treatment outcomes and minimize adverse effects.

Summary:

The peptides and peptide based targeted drug delivery systems represent a frontier in pharmaceutical research and development. The versatility of peptides, coupled with innovative design strategies and an understanding of molecular interactions, positions them as indispensable components in the quest for more effective and patient-friendly drug delivery methods. As ongoing research continues to unravel the complexities of peptide-based drug delivery, the pharmaceutical industry stands on the brink of a new era, where precision and efficacy converge to redefine therapeutic interventions. This comprehensive exploration will delve deeper into the nuances of peptide applications, providing insights into their current state, challenges, and the promising future they herald for targeted drug delivery systems.

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