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A REVIEW ON PEPTIDE-BASED DRUG DELIVERY SYSTEM: MECHANISMS, APPLICATIONS, AND FUTURE PERSPECTIVE

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ABSTRACT

Peptides, comprising amino acids with a molecular weight below 10kDa, offer therapeutic advantages over larger biologics, including higher activity, better tissue penetration, reduced immunogenicity, and lower manufacturing costs. They can be sourced naturally from the body, dietary items, or environmental extraction, as well as synthetically produced in laboratories for medical applications. Peptides play a crucial role in cell signaling and can function as hormones, modulators, or disease biomarkers. In drug delivery systems, peptides are valued for their biocompatibility and ability to be engineered for targeted treatment, enhancing efficacy and minimizing side effects. Cell-penetrating peptides (CPPs) are a notable type, facilitating drug entry into cells via endocytosis or direct translocation.

KEYWORDS: Peptides, Drug Delivery System, Natural Peptides, Synthetic Peptides, Applications.

INTRODUCTION

Peptides are amino acids with a molecular weight of less that 10kDa and typically less than 50 units. When compared to the conventional recombinant protein expression techniques needed for larger protein therapeutics have distinct therapeutic advantages over larger biologics, such as higher activity per unit mass, improved tissue penetration, reduced potential for immunogenicity, and lower manufacturing costs. Peptides in contrast to bigger biologics, are structurally flexible molecules that can have highly environment-development conformations and have both structural and biophysical aims.[1]

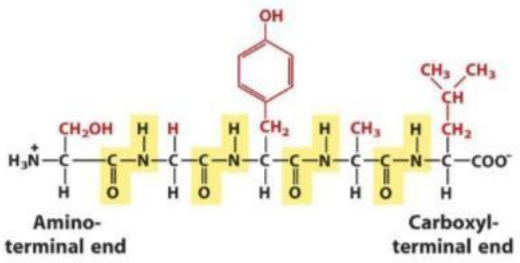


Fig. structure of peptide.[2]

SOURCE OF PEPTIDES

There are two sources to get peptides for pharmaceutical delivery systems: natural sources and synthetic sources. Natural peptides exist in biological systems, and have a multitude of essential actions, including hormones, enzyme substrates or inhibitors, antibiotics and biological regulators . Synthetic peptides, in contrast, can be manufactured via processes such as solid-phase peptide synthesis (SPPS) where the amino acid sequence can be designed and modified as per the requirements. Thus, natural and synthesized peptides are excellent candidates for the creation of peptide-based pharmacological delivery systems with unique biological activities and desired properties.[3]

BIOLOGICAL ROLE OF PEPTIDES:

Peptides are involved in many physiological processes and carry out a variety of biological functions. Their primary function is in cell signalling, where they convey biochemical signals that results in cellular, molecular, structural and physiological impacts. Hormones, agonist, antagonist, modulators, cofactors, activators and stimulators are some of the roles they can play. Certain peptides have antibacterial activity of directly inhibit enzymes by interfering with cellular metabolism and acting on biological membranes or cytoplasmic components. They might function as antigens as well. Furthermore, because they be really, precisely and precisely identified and measured in a variety of body fluids, certain peptides function as disease biomarkers.[4]

PEPTIDE-BASED DRUG DELIVERY SYSTEM:

Peptide-based pharmaceutical delivery systems are drug delivery platforms in which bioactive peptides are conjugated to drugs or carriers or assembled via supramolecular interactions. These peptide-based systems are designed to perform specific functions such as targeted drug delivery and response to changes in the biological environment. Thus, peptides are useful building blocks for developing smart and efficient systems for drug delivery.[5]

WHY PEPTIDES ARE USED IN DRUG DELIVERY SYSTEM?

Peptides are used because of their biocompatibility, affordability, customizable bioactivity, chemical variety, and capacity for precise targeting, peptides are frequently employed in drug delivery systems. Their amino acid sequences can be carefully engineered to achieve desired qualities, and they are readily made. Peptides can help minimize undesired side effects and increase treatment efficacy by delivering medications to diseased tissues in a targeted manner. They are also helpful for targeted and regulated drug delivery because of their capacity to react to particular biological conditions.[6]

TYPES OF PEPTIDE-BASED DRUG DELIVERY SYSTEM:

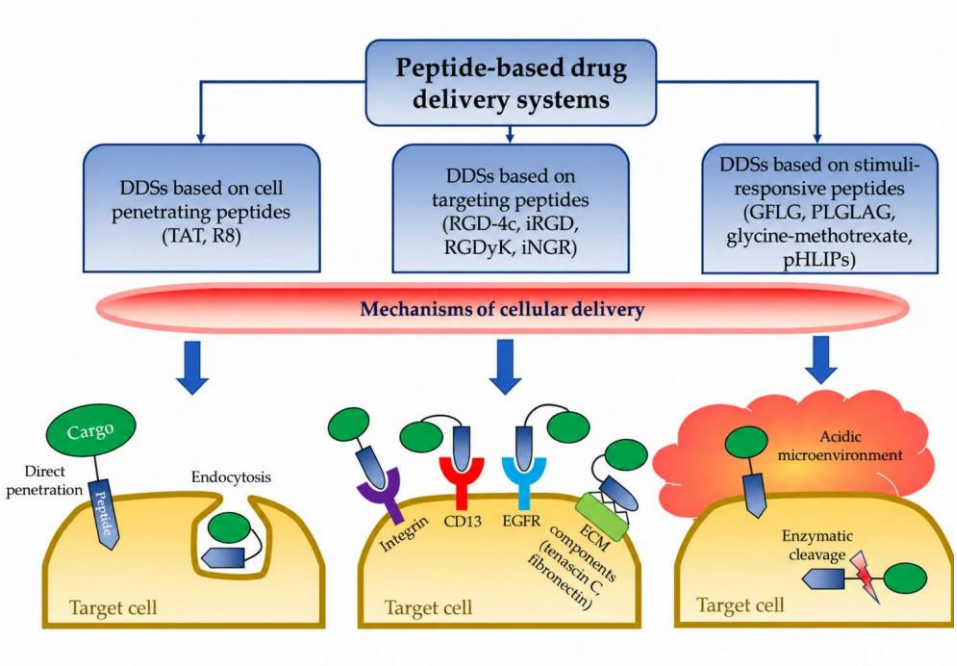


Fig. Types of Peptide Based drug delivery system.[7]

Cell-penetrating peptides: (CPPs) are peptides that interact with cell membranes and are internalized by cells for promotion of intracellular drug delivery. Escobedo et al. prepared polymeric nanogels conjugated with the cell-penetrating peptide Cys-Gly-Lys-Arg-Lys for the delivery of gentamicin to intracellular Pseudomonas aeruginosa in urinary tract infections. The CPP-functionalized nanogels delivered approximately 36% more intracellular gentamicin than free drug in vitro and achieved greater than 90% bacterial clearance in an acute murine model. The study demonstrates that CPP modification can overcome epithelial membrane barriers and improve intracellular antibiotic delivery. Thus, CPPs can enhance the therapeutic performance of drugs that otherwise show poor cellular penetration in difficult intracellular infections successfully.[8]

Tran et al. have studied the intracellular behavior of the cell penetrating peptide p28, particularly its trafficking after cell entry. The study showed that p28 is able to enter cancer cells, but may be trapped in endosomal and Golgi associated compartments, limiting its therapeutic activity Agents such as chloroquine ammonium chloride, and nordihydroguataretic acid changed intracellular trafficking and

increased p28 localization in the cytosol and nucleus Also, chloroquine increased the antiproliferative effect of p28. These results suggest that CPP delivery is not only membrane penetration but also intracellular trafficking and endosomal escape, which should be considered in the design of CPP based systems for drug delivery.[9]

Targeting Peptides: Tang Han, and Mitchell investigated peptide-functionalized nanoparticles for brain-targeted therapeutics, addressing the major challenge of delivering drugs across the blood-brain barrier They describe the incorporation of targeting peptides into nanoparticles that enhance brain accumulation and cellular uptake Among the peptide strategies are receptor-targeting sequences, cell-penetrating peptides, fusion peptides, cyclic peptides, and stereochemcally modified sequences Such modifications may improve the interaction of the nanoparticles with brain endothelial cells and their transfer across biological barriers. Peptide selection and design has a big impact on targeting efficiency, the study notes Peptide-functionalized nanoparticles thus represent a promising strategy for improving site-specific delivery of drugs and miclesc acids to the brain.[10]

Tobi et al. engineered tenascin-C protease activated CendR peptides to improve tumor selective delivery and reduce off-target tissue accumulation. The peptide system was designed to be less active until proteolytic activation reveals the CendR motif and tissue penetration takes place. Another extracellular matrix component associated with tumors and available for targeting of the therapeutic cargo is Tenascin-C. This strategy exemplifies the combination of peptide targeting and enzymatic activation toward enhanced spatial selectivity. Such protease-activated targeting peptides could be useful for developing drug delivery mechanisms that respond to disease-associated molecular features, potentially increasing therapeutic accumulation in tumors while reducing off-target exposure in normal tissues.[11]

Stimuli-Responsive Peptides: Mu et al. reviewed stimuli-responsive peptide assemblies designed to respond to internal or external environmental signals. Peptide nanomaterials can be engineered to react to pH, temperature, ions, light, enzymes, reactive oxygen species, or redox conditions. These stimuli can trigger changes in peptide conformation, self-assembly, size, or morphology, allowing controlled drug release at diseased sites. In drug delivery, such systems may remain stable under physiological conditions and undergo structural changes within tumor microenvironments. The review emphasizes single-, dual-, and multi-stimulus systems, demonstrating how peptide design can provide spatiotemporal control over therapeutic delivery and improve specificity, stability, and treatment efficiency in applications.[12]

Kelly et al. developed a pH-responsive targeting strategy using pH-low insertion peptide (pHLIP) to deliver antigenic MHC-binding peptides selectively into acidic tumor environments. The system exploits the lower extracellular pH characteristic of tumors, where pHLIP undergoes a conformational transition and inserts into cell membranes. This mechanism enabled delivery of antigenic peptides into the cytoplasm of melanoma cells, followed by presentation through MHC molecules and activation of T cells. The study demonstrates how an environmental stimulus can control peptide-

mediated delivery. Such pH-responsive systems may improve selective transport of therapeutic peptides to tumors while reducing exposure of healthy tissues in clinical applications.[13]

MECHANISM OF PEPTIDE BASED DRUG DELIVERY SYSTEM:

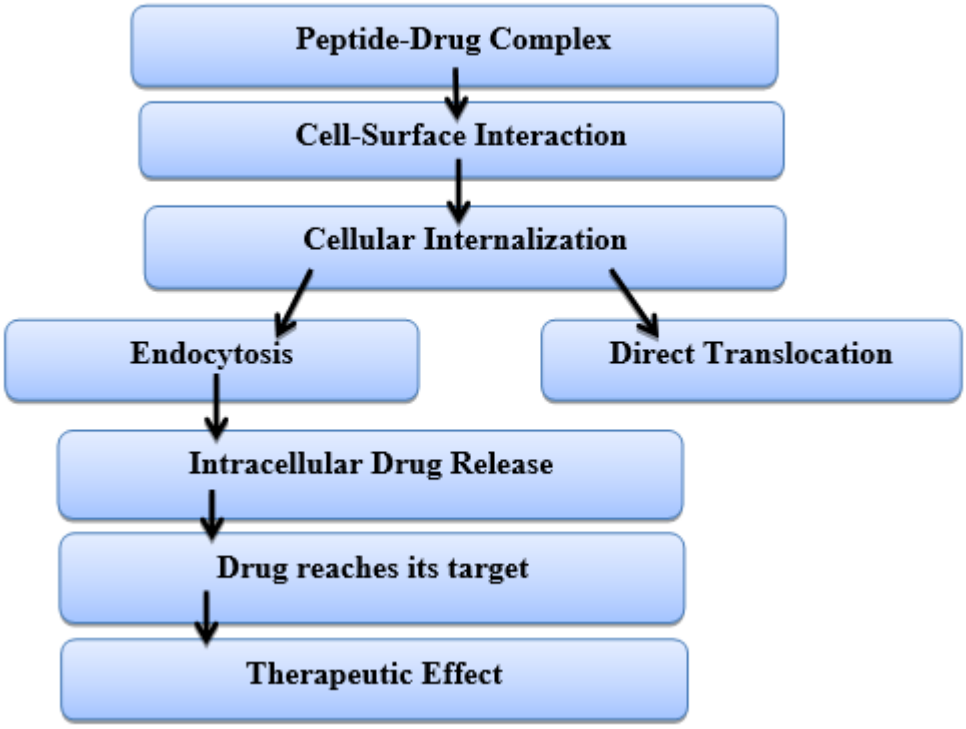


Fig: Flochart of mechanism of peptide based drug delivery system.

The mechanism of peptide-based drug delivery systems generally entails interaction of the peptide with the cell membrane, cellular internalization, intracellular trafficking, release of the therapeutic cargo, and subsequent action at the desired cellular site. These systems facilitate the transport of therapeutic molecules across biological barriers and promote their delivery into target cells. The peptide-drug complex first makes contact with the target cell's surface. Positively charged amino acids, especially arginine and lysine, are found in a large number of cell-penetrating peptides (CPPs). Proteoglycans and membrane-associated molecules, which are negatively charged elements of the cell surface, interact electrostatically with these positive charges. This contact starts cellular uptake and makes it easier for the peptide to adhere to the cell membrane.[14] Endocytosis and direct membrane translocation are the two main ways that the peptide-drug combination can enter the cell after interacting with the cell membrane. The peptide-drug combination is surrounded by the cell membrane during endocytosis, creating an intracellular vesicle known as an endosome. Peptide uptake may be facilitated by various endocytic routes, including as macropinocytosis, clathrin-mediated endocytosis, and caveolae-mediated endocytosis. In direct translocation, the peptide passes thru the cell membrane by means of hole creation or transient membrane instability.[15] The peptide-

drug combination may stay inside the endosome after entering the cell thru endocytosis. For effective intracellular drug delivery, escape from the endosomal compartment is crucial. Certain peptides have the ability to damage or destabilize the endosomal membrane, which permits the therapeutic cargo to enter the cytoplasm. The cargo may stay stuck and its therapeutic effectiveness may be diminished in the absence of effective endosomal escape.[16] The therapeutic payload becomes accessible at the necessary intracellular spot after effective intracellular delivery. The medication may then have the intended pharmacological effect by interacting with its particular molecular target, such as a receptor, enzyme, or nucleic acid. Therefore, peptide-based administration can improve therapeutic compounds' intracellular availability and cellular uptake.[17]

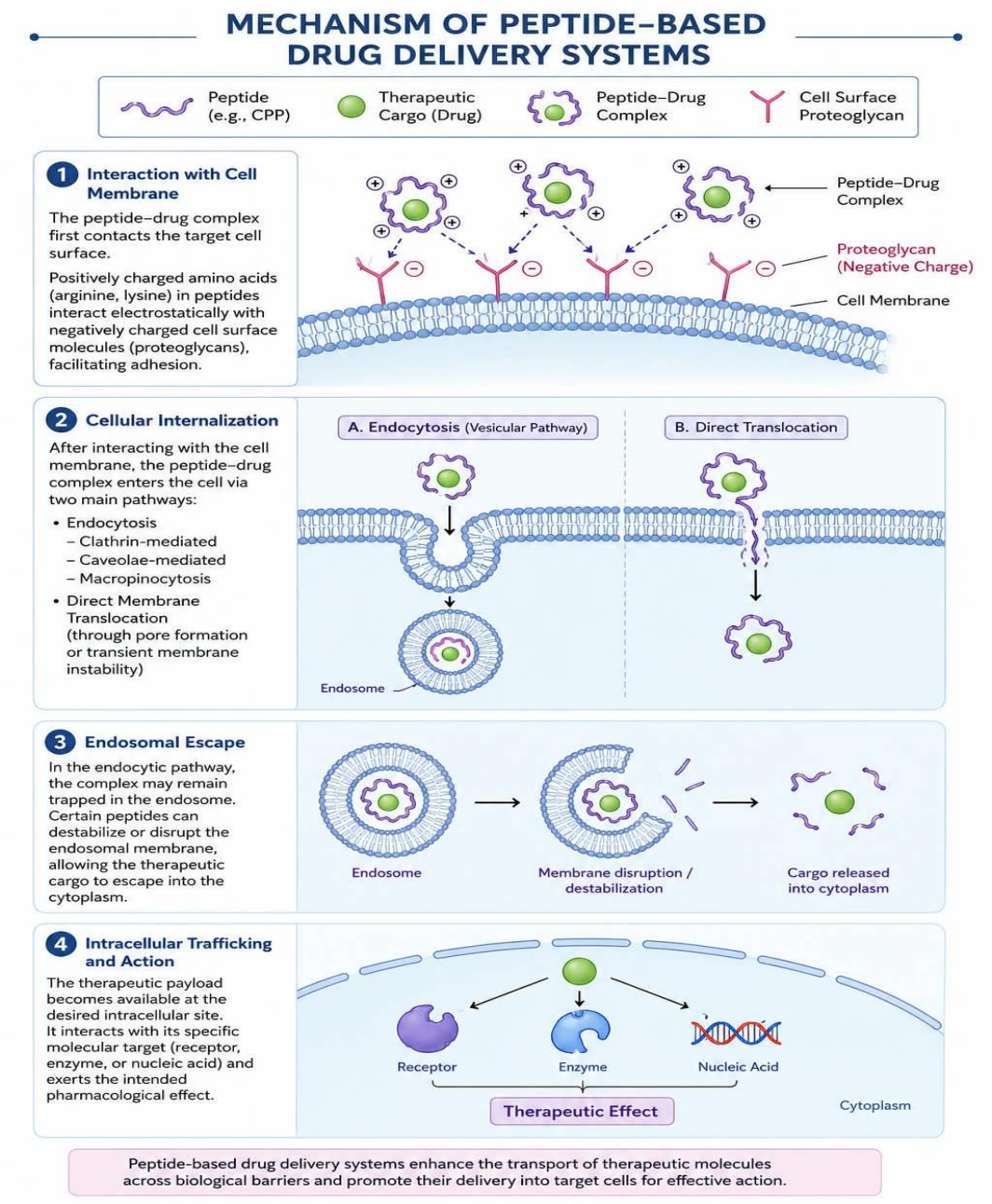


Fig. mechanism of peptide based drug delivery system.

APPLICATIONS OF PEPTIDE-BASED DRUG DELIVERY SYSTEMS IN DISEASE:

Peptide based drug delivery systems have applications in cancer therapy because peptides can enhance the targeting and intracellular and intracellular delivery of anticancer drugs, peptide based drug delivery systems have important uses in cancer therapy. Targeting peptides have the ability to selectively interact with receptors including somatostatin, transferrin and epidermal growth factor receptors that are overexpressed on tumor cells. The therapeutic agent's cellular uptake and tumor targeting may be improved by this receptor mediated interaction. Additionally, peptides can be employed as cell penetrating peptides to deliver therapeutic compounds and anticancer medications into cells. Peptide based delivery methods may thereby lessen adverse medication accumulation at tumor locations.[18]

In order to improve the distribution of peptide treatments for diabetes such as glucagon like peptide 1 receptor agonists (GLP-1RAs) peptide based delivery methods are also crucial in the treatment of daibetes. Enzymatic breakdown, low membrane permeability and restricted oral bioavailability are common issues with peptide medications. To enhance these medications stability, absorption and therapeutic efficasy, various administration methods are being researched. The promise of sophisticated delivery methods for peptide medications in type 2 diabetes was shown by the approval of oral semaglutide.[19]

Due to the biological activity and high specificity of peptides, peptide based drug delivery methods also exhibit promise in cardiovascular disorders. For cardiovascular applications many peptide based delivery methods, including carrier systems such liposomes, have been studied. The stability, targeting and therapeutic availabilty of peptide based medicines can all be enhanced by the creation of peptide delivery systems. Cardiovascular illnesses continue to be a significant field of research for peptide based drug delivery systems, according to recent literature.[20]

RECENT ADVANCES IN PEPTIDE BASED DRUG DELIVERY SYSTEM:

Another important development is the use of cell targeting peptides (CTPs) and cell penetrating peptides (CPPs). These peptides could be used to target drugs to specific cells and to improve the transport of therapeutic molecules across cell membranes. Research on the delivery of pharmaceuticals, nucleic acids and nanocarriers with CPP-based platforms. Recent clinical research on CPP-based delivery systems has been directed to imaging applications, cancer and cardiovascular diseases. More recently, structural modification to improve peptide stability and pharmacokinetics properties has also been reported. Researchers are changing the peptide architecture to reduce degradation and clearance, while maintaining biological activity and target selectivity. These advances are aimed at improving patient compliance, reducing dose frequency and increasing the half-life of peptide drugs Peptide-drug conjugates, or PDCs, are another significant recent advancement. [21]

One of the main developments of peptide based drug delivery is the creation of peptide-drug conjugates (PDCs), by conjugating medicinal pharmaceuticals with functional peptides to enhance targeted delivery. The peptide moiety can impart targeting or cell penetrating properties that will help the therapeutic payload reach the desired tissue/cells more efficiently. PDCs have gained substantial interest because of their comparatively tiny size and peptide-mediated targeting that may lead to improved tissue penetration, drug localization and therapeutic efficacy. Such systems have been researched notably for delivery of anticancer drugs and nucleic acid-based therapies.[22]

Ma et al. reviewed the recent strategies for enhancing the therapeutic efficacy of peptide-drug conjugates (PDCs), with an emphasis on the improvements in targeting precision, stability, permeability, and payload design. Modern PDC development includes multivalent and bispecific targeting, long-acting conjugates, improved protease resistance, new payloads and approaches to overcome biological barriers. cell-targeting peptides can trigger receptor-mediated internalization, and cell-penetrating and stimuli-responsive peptides can improve intracellular delivery and controlled release. These developments indicate that PDCs are progressing from simple peptide-payload constructs to multifunctional delivery systems. Further optimization of peptide sequences, linkers, pharmacokinetics and tumor selectivity may translate to wider clinical translation in practice and further improvement of therapeutic efficacy.[23]

Recent progress in peptide-based nanocarriers for targeted drug delivery including liposomes, solid lipid nanoparticles, dendrimers, polymeric micelles, mesoporous silica nanoparticles and hybrid systems was discussed by Adnan et al. Peptides can serve as targeting ligands, structural parts, cell penetrating moieties or stimuli-responsive motifs. Recent advances include cyclic and stapled peptides, biodegradable carriers, co-delivery platforms and intelligent systems responsive to pH, enzymes or redox gradients. The review also highlights its use in cancer, neurological disorders, infectious diseases, inflammation, and nucleic-acid delivery. New artificial intelligence and computational approaches may speed up the optimization of peptide sequences. But stability, immunogenicity and manufacturing and regulatory hurdles remain important challenges for clinical translation.[24]

Recent progress in peptide drug delivery has been dedicated to solving the problems of low metabolic stability and short half-life of peptide therapeutics. Other approaches include structural alterations such peptide stapling and incorporation of D-amino acids to enhance resistance to enzyme degradation and stability of peptides. Novel delivery techniques and cell-penetrating peptides are also being explored to improve delivery of peptide therapeutics to their target areas. These techniques may be effective to improve the biological activity of peptides and to enhance their medicinal potential.[25]

FUTURE PERSPECTIVE OF PEPTIDE BASED DRUG DELIVERY SYSTEM :

Future studies can be focused on emerging technologies such as 3D printing, hydrophobic ion pairing and self nanoemulsifying pharmaceutical delivery system (SNEDDS) for improvement of oral peptide

administration. The approaches may improve peptide stability, intestinal permeability and bioavailability. Additional research are needed to optimize the qualities of the formulation, its safety, repeatability, and scalability for a successful clinical use.[26]

Microbiome-based administration is a promising avenue for oral peptide therapies. Microorganisms can be designed to secrete therapeutic peptides directly in the gastrointestinal tract, which may improve stability and enable targeted delivery. Future study should focus on the management of peptide production, the safety of the microorganisms and the assessment of the long term impact on the intestinal microbiota.[27]

Further development of peptide delivery systems should focus on successful clinical translation of advanced oral formulations. Better protection against GI breakdown, intestinal permeability and therapeutic exposure is still needed. Additional research should evaluate variability in pharmacokinetics, long-term safety, reproducibility of fabrication, and patient outcomes to develop reliable and therapeutically feasible options for injectable peptide therapies.[28]

CONCLUSION

Peptide based systems for drug delivery are promising approaches for enhancing the delivery of therapeutic drugs. Peptides present advantages of biocompatibility, precise targeting, and tunable bioactivity to facilitate the delivery of drugs to specific tissues/cells. Peptide-based systems including cell-penetrating, targeting and stimuli-responsive peptides provide several strategies for efficient drug delivery. These approaches may boost intracellular drug release and cellular uptake to improve the therapeutic efficacy.

Their use in conditions such as cancer, diabetes and cardiovascular ailments shows their potential in targeted therapy. Improvements such as peptide-drug conjugates, peptide stability and new delivery methods are overcoming limitations including short half-life, enzymatic degradation and low oral bioavailability. Additional studies on the enhanced stability, bioavailability, targeting and utilization of advanced technologies like artificial intelligence may greatly improve the efficacy and convenience of peptide-based drug delivery methods in the future.

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