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A Review on Oral and Transdermal Protein Delivery System

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ABSTRACT: The delivery of protein and peptide drugs presents a significant challenge due to their complex structure, poor stability, and low oral bioavailability. With a focus on overcoming physiological and biochemical barriers, this review examines the most recent approaches for oral and transdermal protein delivery systems. It emphasizes the functions, digestion, and structure of proteins as well as the illnesses brought on by protein deficiencies. The functions of several drug delivery technologies, including PEGylation, iontophoresis, liposomes, nanoparticles, and microneedles, in improving protein delivery are thoroughly examined. The use of absorption enhancers, enzyme inhibitors, mucoadhesive systems, and ligand modifications to improve drug stability and absorption are also covered in the review, along with biomaterials such as hydrogels, nanogels, and scaffolds. The potential for controlled, non-invasive drug release is assessed for transdermal delivery systems, including passive and active techniques. Advanced advancements in transdermal insulin delivery receive particular attention. All things considered, this review offers an in-depth understanding of the most recent developments, technologies, and potential applications in oral and transdermal delivery of proteins and peptides.

KEYWORDS: Protein and Peptide drug delivery, Oral delivery, Transdermal delivery

I. INTRODUCTION

Proteins are complex biomolecules made up of α-peptide bonds connecting amino acids. In the human body, they carry out essential functions such as immunological responses, hormonal regulation, enzymatic activity, and structural support. Only the primary amino acid sequence matters nutritionally, and only 20 of the body's numerous amino acid-like compounds are encoded by DNA, though a few others have important physiological functions. Dietary proteins are broken down in the digestive system, absorbed as peptides and amino acids, andused for other metabolicprocesses, including cellular protein synthesis.Drugs containing proteins and peptides are attracting interest because of their strong therapeutic effects and high specificity. However, due to their large molecular size, short systemic half-lives, poor permeability across biological membranes, and susceptibility to enzymatic degradation, their delivery presents significant challenges. Although bioavailability is ensured by traditional parenteral delivery, repeated injections frequently result in low patient compliance. As a result, other delivery methods like oral and transdermal are being investigated.

Convenience makes oral delivery the preferred method; however, poor absorption and enzymatic degradation result in low bioavailability. Bypassing the gastrointestinal tract and first-pass metabolism, transdermal delivery, on the other hand, provides a non-invasive substitute that improves patient compliance and offers a sustained release.

The challenges and approaches related to oral and transdermal protein and peptide drug delivery are thoroughly examined in this review. It covers a range of enhancement methods, such as PEGylation, enzyme inhibitors, microneedles, nanotechnology, and mucoadhesive systems. It also showcases recent developments in transdermal insulin delivery, which indicates well for non-invasive protein-based treatments in the future.[1]

PROTEIN AND PEPTIDE DRUG DELIVERY SYSTEM

L-α amino acids are polymerized by peptide bonds to produce the fundamental structure of proteins, which are strings of amino acids joined by covalent connections. Peptides are particles composed of less than50amino acids, whereas proteins are composed of around 50 amino acids.[2] Peptides are made for a wide variety of

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molecules and have many applications in areas including immunology, infectious disorders, endocrinology, and cancer. The primary component of proteins and peptides, which are biopolymers containing two or more amino acids upon hydrolysis, is the cell's protoplasm. Because of their enzymatic barrier, protein peptides may not have clinically appropriate bioavailability when administered orally.[3] Pharmaceutical developers are always drawn to these medications because of their broad range of activity, excellent potency, and selectivity in spite of these difficulties. An overview of the main development techniques, motivators, and restrictions on inappropriate use of protein and peptide therapies is given in the current material.[4]

ADVANCED TECHNIQUE OF PROTEIN AND PEPTIDE DRUG DELIVERY

- Pulmonary drug delivery
- Transdermal technology
- Microneedle technology
- Thermal ablation
- Oral delivery of peptides
- Ionotophoresis
- Electroporation
- PEGylation

Pulmonary drug delivery

Protein and peptide therapy can be administered non-invasively by pulmonary drug administration, which avoids the gastrointestinal tract and hepatic metabolism. Nebulizers, metered dosage inhalers, and dry powder inhalers are some of the methods. Carriers based on nanoparticles improve bioavailability and stability. Lung residence duration isextended by mucoadhesive agents and PEGylation.[5]

Transdermal technology

Benefits of transdermal drug delivery (TDD) include enhanced protein and peptide bioavailability and a constant plasma profile. Methods for overcoming the difficult obstructive work of the skin are suggested. The Macroflux Ep-i transdermal fix innovation increases adequacy and bioavailability without giving patients a great deal of distress. Because proteins and peptides have less probiotic activity, this technique is especially appealing for them.

Microneedle technology

Drug molecules can coagulate through aqueous channels made in the skin using microneedle scopes, which bypass the stratum corneum barrier. They may be employed for transdermal drug administration, and each variety has unique points and barriers. The quantity of medication that can be obtained using electrical micro heaters and radiofrequency removal is restricted by the small surface area of coated microneedles, despite the fact that they provide a more effective approach.[6]

Thermal ablation

In order to improve medication delivery, thermal ablation involves heating the skin's surface for a few milliseconds. Without harming the surrounding tissues, this mechanism creates microscale pores and breaks down water in the stratum corneum. The Pass Port® repair, a patented invention from Altea Therapeutics, heats the skin's surface with an electric pulse to induce local disintegration. Studies on animals have successfully employed this technique.[7]

Oral delivery of peptides

The physical and chemical characteristics of peptides, such as their molecular size, enzymatic degree, plasma half-life, ion permeability, immunogenicity, and aggregation, adsorption, and denaturation, make ingestion difficult. Oral bioavailability is further influenced by physiological parameters such as intestinal bacteria, stomach-related enzymes, pH, travel time, gastric tiredness, and epithelial vehicle. By passing the medication via the digestive system, oral drug delivery techniques shield the medication from enzymatic breakdown. Despite possible health risks, artificial modifications like as protease inhibitors or publication enlargement can increase protein bioavailability. Certain polymers can be used orally to protect peptides from corrosive and compound attacks.[8]

Ionotophoresis

Ionotophoresis is an invasive technique that delivers medications via the skin using a moderate electric current. This century-old invention has been impacted by developments inrecombinant DNA technology, microelectronics, and latent transdermal medications. Insulin has been administered to diabetic rats by Electrical iontophoresis, and an implantable device termed Electrical Repair Instrument has been created for parasitic animals. β-blockers have been administered using pulse electric iontophoresis without causing skin discomfort. Iontophoresiscan

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lead to the utilization of proteins or peptide drugs.[9]

Electroporation

Benefits of electroporation include in vivo performance, efficiency, small size, and adaptability. However, too strong or prolonged pulses may harm cells, and nonspecific transport during electro permeability may result in unequal particle distribution, which may lead to poor cell capacity and transit. Therefore, increasing medication delivery through the skin requires careful thought and the development of efficient electroporation techniques.[10]

PEGlytion

PEGylation is a well-studied technique for parenterally delivering special proteins and peptides. By altering characteristics like weight, dimensions, and steric barrier, it improves the stability, pharmacokinetics, and restorative motions of these medications. The FDA has authorized PEGylation for infusion utilizing biotechnological pharmaceuticals since it is non-immunogenic, low protein/cell adsorption, and nontoxic. Although it frequently results in a loss of natural mobility, the improved security and hydrodynamic volume make up for this by delaying body-home time.[11]

NANOPARTICLE:ORAL DELIVERY FOR PROTEIN AND PEPTIDE DRUG

Protein and peptide medications, which target several receptors worldwide, have been evolving rapidly. These medications can be used to treat or prevent a wide range of illnesses, but they are especially useful for cardiovascular, autoimmune, and cancer conditions. However, chemical and physical instabilities such low pH levels, gastrointestinal tract breakdown, and quick removal from circulation restrict their broad usage. These medicationspoor bioavailability is a significant problem, even though oral administration is essential for improved patient acceptance and disease control. Although these medications are still in the early phases of research and development, nanotechnology has been employed to enhance their usage.[12]

THE ABSORPTION MECHANISM OF NANOPARTICLE AS CARRIERS FOR PROTEIN PEPTIDE DRUG

There are four methods that protein and peptide drug-loading nanoparticles can cross the gastrointestinal membrane: M cell (membranous/microfold cell) transport,receptor-mediated transport, vector-mediated transport, and transmembrane transport. The most significant transmembrane transport cells in the gastrointestinal system are M cells, which enable nanoparticles to enter cells and cross the cell basement membrane via the transmembrane transport route. A mucosal immune response can be triggered by M cells' ability to absorb particles and transfer antigens from the intestinal passageway to lymphoid tissue.Both carrier-mediated and receptor-mediated transports attach to corresponding ligands via intramembrane carriers or membrane receptors, respectively, and are subsequently finished by cytokines or phagocytosis. By altering the ligands in protein polypeptide medications and their capacity to connect with receptors on intestinal cell membranes, these pathways can be changed to enhance drug permeability.In the digestive system, nanoparticles are absorbed by means of endocytosis, which moves them to the intestinal lymph node (Peyer's patches), where they are subsequently taken up by M cells. Additionally, nanoparticles can enter the bloodstream and improve M cells' absorption in Peyer's patches.The bioavailability of protein peptides can be increased by preparing them for administration as oral nanoparticles. Using unique carrier materials, such as bioadhesive enteric release functional microspheres, oral nanoparticles can be enhanced and targeted to the gastrointestinal tract of the Pyle collection of lymph nodes.[13]

METHODS TO PROMOTE THE ORAL DELIVERY OF PROTEIN AND PEPTIDE DRUG NPS

After oral administration, nanoparticles can be absorbed via the gastrointestinal tract (GT); however, poor absorption represents a significant challenge to the development of oral nanoscale drug delivery systems. Paracellular, transcellular, carrier-mediated, and receptor-mediated transport are the four ways that chemicals can pass through cell membranes. Mucous adhesion systems, chemical modification, absorption enhancers, and nanoparticle lists are methods for increasing protein bioavailability.

Absorption enhancers

Peptide absorption via the cell bypass and cell routes can be enhanced by absorption enhancers. While cysteine-modified acrylic polyesters can improve mucosal adherence and release rate, PEG chains can facilitate nanoparticle penetration of the mucilage layer. By binding

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directly to the surface of nanoparticles, a lectin can start endocytosis and increase medication bioavailability. By facilitating the opening of tight junctions between cells, intercellular drug transfer facilitates drug delivery. Oral absorption of peptides and protein medicines is significantly hindered by the breakdown of gastrointestinal digestive enzymes and thelimited permeability of intestinal epithelial cells. By altering cell integrity, expanding intercellular gaps, or upsetting the stability of the lipid bilayer, absorption enhancers can rapidly penetrate the intestinal barrier and improve the absorption of protein peptide drugs into the bloodstream through the gastrointestinal tract.[14]

Enzyme inhibitors

Protein and peptide medications can be better absorbed by using enzyme inhibitors that inhibit their breakdown in the digestive system. The bioavailability of these inhibitors is greatly increased when taken orally. Leupeptin, sodium glycocholate, bacitracin, bestatin, and cystatin are examples of protease inhibitors that can improve the effectiveness of insulin in the large intestine. It is possible to encapsulate enzyme inhibitors in nanoparticle systems, which improves absorption and protects medications from enzyme degradation. Long-term usage, however, may result in the absorption of protein breakdown and significant toxicity. Drug bioavailability is increased when absorption enhancers and enzyme inhibitors are combined.[15]

Mucoadhesive

By enhancing mucous membrane adhesion, the gastrointestinal tract's mucous layer can enhance medication absorption and effectiveness. By changing the permeability of the mucous epithelium and raising the concentration of the medication, mucosal adhesion nanoparticles can improve drug absorption. Mucous adhesives can also improve stability, regulate release rates, and prevent the breakdown of protein peptides. Because of their longer retention period and capacity to adhere to the mucus layer, mucous adherence nanoparticles (MNPs) may be an appropriate nanocarrier for protein and peptide medications.[16]

TRANSDERMAL DELIVERY OF PROTEIN

According to developments in recombinant DNA technology, protein-based medications are essential for the treatment of diseases including cancer,osteoporosis, and diabetes. Because proteins are polar and complex molecules with high molecular weights, they are challenging therapeutic candidates to distribute. The parenteral route is now the main method used to give proteins; however, it presents limitations, including gastrointestinal breakdown, limited bioavailability, and local discomfort. Although the stratum corneum barrier restricts the distribution of hydrophilic proteins, the skin provides an alternate route for transferring proteins into the systemic circulation.Proteins are Chemical enhancers, iontophoresis, microneedles, sonophoresis, laser ablation, thermal ablation, radiofrequency ablation, jet injectors, and electroporation are some of the enhancement techniques that have been studied in an effort to get over this challenge. These methods allow for a variety of drug delivery methods with ≥50% bioavailability. When compared to the parenteral method, the transdermal approach may yield greater bioavailability and cost-effectiveness.[17]

FORMULATION APPROACHES

For medications that wouldn't passively flow through the skin, chemical enhancers can change the stratum corneum's lipid composition, decreasing its barrier qualities and increasing permeability. Ethanol and cineole, for instance, can enhance the transdermal transport of the hormone that releases thyrotropin. It has also been noted that combination of certain peptide sequences, which function as peptide facilitators, increases peptide delivery. It has been attempted to improve medication distribution by chemically altering peptides, such as lipophilic derivatives, although this may have an impact on pharmacological efficacy. It has also been shown that peptide encapsulation improves distribution via the skin. Larger proteins require alternative techniques because current enhancing techniques are only effective on short peptides.[18]

IONOTOPHORESIS MEDIATED TRANSDERMAL DELIVERY OF PROTEIN

Iontophoresis is being studied for systemic administration after being found to be an effective localized medication delivery method in physical therapy clinics. Proteins and other charged medicinal molecules are propelled into the skin by moderate current. Electroosmosis (EO) and electromigration (EM) are the primary transport processes. About 70% of the transport of the model peptide D-(Arg)-kyotorphin occurs by electromigration. However, each mechanism's contribution alters significantly when adhesive

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removing modifies skin permselectivity. Iontophoretic delivery depends on a number of factors, including protein size, charge, structure, and lipophilicity, as well as experimental parameters like electrodes and current density.[19]

ELECTROPORATION

The process of electroporation modifies cell membranes in a reversible way to transfer macromolecules, such as DNA, into cells. It involves briefly delivering high voltage pulses to increase the permeability of cell membranes and create aqueous pores. This technique has been investigated for transdermal drug delivery, delivering peptides and proteins. Higher voltages over 50 V are needed for skin electroporation, which has been demonstrated to be successful in increasing epidermal Langerhans cell migration and delivering therapeutic quantities of peptides. At high voltages, however, skin characteristics may change, resulting in a complex flux-voltage dependence. High concentrations of a number of proteins and peptides have been observed when electroporation is combined with other enhancing techniques, such as iontophoresis.[20]

SONOPHORESIS

The process of sonophoresis creates skin permeability by creating turbulence in the stratum corneum layer using low-frequency ultrasonic vibrations. In physical therapy clinics, this procedure is used to relieve pain and distribute proteins and peptides such as erythropoietin, insulin, heparin, γ-interferon, hormones, and oligoneucleotides. The SonoPrep®technology, created by Alpha Therapeutics, increases insulin delivery in the animal model by creating cavitation with short pulses of ultrasonic waves. However, its practically for self-use is limited.[21]

ADVANCES IN TRANSDERMAL INSULIN DELIVERY

Diabetes mellitus is a metabolic disorder that causes excessive blood glucose accumulation due to increased liver glucose synthesis and reduced muscle and fat clearance. The number of cases is predicted to increase globally, affecting around 425 million individuals. The inability of the pancreas to secrete insulin or the body's impaired sensitivity to insulin are the two main causes of type 1 diabetes. The management of both type 1 and advanced type 2 diabetes requires the use of exogenous insulin.Frequent injections, however, may be linked to microbial contamination and poor adherence. Transdermal delivery and other needle-free options have been explored as solutions to these problems. Compared to oral, pulmonary, and nasal administration, transdermal distribution has the advantages of prolonged release, avoiding digestive system degradation, and improving patient adherence. Skin barriers, however, continue to make it difficult to administer insulin through the skin effectively.[22]

Chemical enhancers promoted transdermal delivery

In order to increase skin permeability and transport medicines, chemical penetration enhancers have been thoroughly studied. By causing lipid-packing errors and rupturing the epidermal barrier, these enhancers can increase the transport efficiency of insulin. The permeation enhancement characteristics of forty-three chemical enhancers utilized in insulin administration were investigated by the Gasem group. By decreasing disulfide linkages, inactivating endogenous sulfhydryls, and maintaining insulin potency, iodine made it easier for insulin to be delivered via the skin. Transdermal insulin administration was also improved by trypsin's capacity to interact with the stratum corneum.[23]

Electrically facilitated transdermal delivery

Electrical devices that help move insulin through the skin have also drawn a lot of studies, in addition to chemical penetration enhancers. In contrast to chemical penetration enhancers, these electrical devices increase the effectiveness of insulin delivery through the skin by either causing a brief disruption of the stratum corneum by a high-voltage electrical pulse or by supplying an extra driving force through electrical interactions.[24]

Mechanical force triggered insulin delivery

Another option for creating temporary channels on the skin's surface for transdermal drug administration, in addition to electrical fields, is mechanical force. The two most commonmechanical force-triggered techniques for delivering insulin are ultrasound and jet injection. Through the cavitation effect or hyperthermia, ultrasound can increase the permeability of medications throughthe skin. In order to administer insulin solution into the skin tissue, jet injection uses a high-speed liquid to break down the skin's surface.[25]

II. CONCLUSION

Protein polypeptides can be chemically modified to improve medication stability, decrease

immunogenicity, increase membrane permeability, and decrease bioactivity. Although they can increase gastrointestinal toxicity, absorption enhancers can also improve medication absorption in the small intestine. Although mucosal adhesion systems can enhance bioavailability and extend drug retention, they are unable to improve oral permeability or prevent the small intestine mucosa from being cleaned. Because of their benefits, but also because of their high preparation costs and challenging expanding properties, nanoparticles are being investigated as oral delivery vehicles.Particle size, surface charge, hydrophobicity, and drug loading capacity are some of the variables that go into creating nano-microspheres. Due to considerations including loading capacity, loading method, and medication physicochemical qualities, the ideal combination of parameters has not been optimized. With a number of new and developing technologies that can currently facilitate the transfer of hydrophilic macromolecules over the skin, the transdermal method for delivering protein therapies is being intensively investigated. There are a few active/physical enhancement products on the market right now, and many are in the development and clinical testing stages.

REFERENCE

[1]. Jain S, Jain A, Gulbake A, Shilpi S, Hurkat P, Jain SK. Peptide and protein drug delivery through skin. Drug Discov Today. 2015 ;20(2):295-301.
[2]. Bhargav E. 2017. An over view: Protein and peptide based drug delivery. International Journal of Pharmaceutical Sciences Review and Research, 42:169–178.
[3]. Gupta H, Sharma A. 2009. Recent trends in protein and peptide drug delivery systems. Asian Journal of Pharmaceutics, 3(2):69–75.
[4]. Agyei D, Ahmed I, Akram Z, Iqbal HMN, Michael KD. 2017. Protein and Peptide Biopharmaceuticals: An Overview. Protein & Peptide Letters, 24(2):94–101.
[5]. Aggarwal S, Sharma S, Lal S, Choudhary N. 2018. Protein and Peptide Drug Delivery : By Noninvasive Technology. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 8(470):470–476.
[6]. Chandrasekhar S, Iyer LK, Panchal JP, Topp EM, Cannon JB, Ranade VV. 2013. Microarrays and microneedle arrays for delivery of peptides, proteins, vaccines and other applications. Expert Opinion on Drug Delivery, 10(8):1155–1170.
[7]. Kalluri H, Banga AK. 2011. Transdermal delivery of proteins. AAPS PharmSciTech, 12(1):431–441.
[8]. Mahato RI, Narang AS, Thoma L, Miller DD. 2003. Emerging trends in oral delivery of peptide and protein drugs. Critical Reviews in Therapeutic Drug Carrier Systems, 20(2–3):153–214.
[9]. Ratnaparkhi MP, Chaudhari SP, Pandya Va. 2011. Peptides and proteins in pharmaceuticals. International Journal of Current Pharmaceutical Research, 3(2):1–9.
[10]. Lakshmi PK, Prasanthi D, Harini K. 2017. Noninvasive delivery of protein and peptide drugs: A review. Asian Journal of Pharmaceutical and Clinical Research, 10(8):25–33.
[11]. Veronese FM, Pasut G. 2005. PEGylation, successful approach to drug delivery. Drug Discovery Today, 10(21):1451–1458.
[12]. Rekha MR, Sharma CP. Oral delivery of therapeutic protein/ peptide for diabetes–future perspectives. Int J Pharm.2013;440:48–62.
[13]. Yun Y, Cho YW, Park K. Nanoparticles for oral delivery: targeted nanoparticles with peptidic ligands for oral protein delivery. Adv Drug Deliv Rev. 2013;65:822–32.
[14]. Renukuntla J, Vadlapudi AD, Patel A, Boddu SH, Mitra AK. Approaches for enhancing oral bioavailability of peptides and proteins. Int J Pharm. 2013;447:75–93.
[15]. Ibraheem D, Elaissari A, Fessi H. Administration strategies for proteins and peptides. Int J Pharm. 2014;477:578–89.
[16]. Duggan S, Cummins W, O'Donovan O, Hughes H, Owens E. Thiolated polymers as mucoadhesive drug delivery systems. Eur J Pharm Sci. 2017;100:64–78.
[17]. Antosova Z, Mackova M, Kral V, Macek T. Therapeutic application of peptides and proteins: parenteral forever? Trends Biotechnol. 2009;27(11):628–35.
[18]. Jain S, Jain P, Umamaheshwari RB, Jain NK. Transfersomes—a novel vesicular carrier for enhanced transdermal delivery: development, characterization, and performance evaluation. Drug Dev Ind Pharm. 2003;29(9):1013–26.
[19]. Abla N, Naik A, Guy RH, Kalia YN. Contributions of electromigration and electroosmosis to peptide iontophoresis across intact and impaired skin. J Control Release. 2005;108(2–3):319– 30.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2123-2129 www.ijprajournal.com ISSN: 2456-4494

[20]. Edwards DA, Prausnitz MR, Langer R, Weaver JC. Analysis ofenhanced transdermal transport by skin electroporation. J Control Release. 1995;34:211–21.
[21]. Tezel A, Dokka S, Kelly S, Hardee GE, Mitragotri S. Topicaldelivery of anti-sense oligonucleotides using low-frequency sonophoresis. Pharm Res. 2004;21(12):2219–25.
[22]. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE, Global estimates of diabetes prevalence for 2013 and projections for 2035, Diabetes Res. Clin. Pract, 103 (2014) 137–149.
[23]. Finnin BC, Morgan TM, Transdermal penetration enhancers: applications, limitations, and potential, J. Pharm. Sci, 88 (1999) 955–958.
[24]. Denet A-R, Vanbever R, Préat V, Skin electroporation for transdermal and topical delivery, Adv. Drug Del. Rev, 56 (2004) 659–674.
[25]. Zhang Y, Yu J, Bomba HN, Zhu Y, Gu Z, Mechanical force-triggered drug delivery, Chem. Rev, 116 (2016) 12536–12563.