NARRATIVE REVIEW

Routes and barriers associated with protein and peptide drug delivery system

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Abstract

Proteins and peptide drugs have a great therapeutic potential and their usage in the treatment of various severe diseases has revolutionised the fields of pharmaceuticals and biotechnology. For successful therapeutic effects, various efforts have been made for effective delivery of proteins/peptide drugs through various routes of administrations. Parenteral and non-parenteral drug deliveries are regarded as significant routes of drug absorption. In addition to intravenous, subcutaneous and intramuscular routes, the oral route is more effective for protein and peptides therapeutics. However, there is a need to improve non-parenteral drug delivery systems (DDS) to increase drug absorption in a more effective way. The present narrative review was planned to describe routes and barriers for protein/peptide drugs and how to improve drug delivery systems in an effective way. For this purpose, numerous research articles were searched from year 2000-2021 using search engines like PubMed, Google Scholar, Medline and ISI Web of Knowledge, and Bioline International while applying different keywords such as 'protein and peptide drugs', 'drug delivery systems', 'parenteral and non-parenteral routes of drug delivery' and 'physicochemical barriers'. It was concluded that the success of the therapeutics is strongly influenced by the differential delivery of targeted antigen, the choice of targeting protein or peptide, and drug-release characteristics of the linker used. Furthermore, there should be an improvement in non-parenteral DDSs so that the drugs might be administered in an appropriate manner.

Keywords: Protein, Peptide, Drug delivery system, Parenteral drug delivery, Non-parenteral drug delivery, physico-chemical barriers.

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Introduction

Protein are abundant organic molecules in a living system. They are composed of more than 50 amino acid. Protein are blended polymers of alpha amino acids with high molecular weight, joined together by peptide linkages. Proteins, being an imperative part of the living cell, assist in nutritional activity and tissue-building ability of our body.

Proteins perform vital roles, such as enzymatic catalysis, gene regulation, and signal transduction; and sustain a fine stability among cell's persistence and cell's demise.[1] Similarly, they act as enzymes to catalyse biochemical reactions, and control metabolic pathways, temperature, potential of hydrogen (pH) and osmotic pressure. The protein named "insulin" regulates blood sugar level.[2]

Peptides have less than 50 amino acids, and are mainly condensation products of amino acids which result in dipeptides, tripeptides, tetrapetides and polypeptides. Proteins and peptides, being copious materials of biological cells and living systems, are considered as novel approaches for the delivery of protein and peptide therapeutics. These have a significant role in immunogenic defence mechanism, metabolically active processes, and biological activities. Numerous hormones and peptides are important for pharmaceuticals and biopharmaceuticals. The prime applications of proteins and peptides have been extensively observed in medical practices, drug discovery processes and research activities.[3]

There are two main routes of any drug delivery system (DDS). Parenteral systemic delivery is used for systemic delivery of proteins and peptides, and non-parenteral systemic delivery comprises subsequent routes, like buccal, pulmonary, oral, ocular, transdermal, and nasal routes.[4] Biotechnological progress is applied for development/synthesis of many therapeutic and antigenic peptides and proteins, offering improved research ad application options for pharmaceutical scientists. Proteins and peptides have imperfect absorption due to their critical physicochemical properties, including susceptibility to enzymatic degradation and poor permeability across intestinal mucosal membranes.[5] The current narrative review was planned to evaluate various DDS routes proposed for the distribution of proteins and peptides along with various barriers associated with drug administration.

Methodology

In this article, an extensive search was carried out to review numerous studies linked to different routes of proteins and peptides drug delivery systems as well as their associated

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barriers for successful administration. Original research articles were searched using search engines like PubMed, Google Scholar, Medline and ISI Web of Knowledge, and Bioline International while applying different keywords such as 'protein and peptide drugs', 'drug delivery systems', 'parenteral and non-parenteral routes of drug delivery' and 'physicochemical barriers' during the years 2000-2021. Around 94 full text research articles which included different routes of drug delivery, and the barriers that are associated with drug delivery systems were initially downloaded. However, as the search process was limited to articles in English language only, 14 articles were exclude for having non-English communication language. The remaining research articles were further screened for relevance with the topic and 17 articles were excluded for their irrelevance with the topic of this review article. Finally, 63 research articles with the most recent and relevant research material were reviewed in detail.

Routes of protein/peptide DDS

Parenteral systemic delivery: Parenteral drug delivery mode is considered as an important route for the delivery of proteins and peptides, and play a vital role to target the receptors. Hence, it has the ability for improvement of drug therapeutic index. Protein and peptide delivery is somewhat restricted by biological functions; and injections are required owing to the short half-life of proteins. Parenteral drug delivery includes intraperitoneal (IP), intramuscular (IM), intrathecal, intravenous (IV) and subcutaneous (SC) routes of administration.[6,7] The most common routes include IV, IM and SC (Table).[6-9]

Non-parenteral systemic delivery: The bioavailability of drugs deals with the measure of fraction and rate of

Table: Some protein and peptide drugs indicating targeted disease and routes of administration.

Drugs	Targeted disease	Route	Rfr
Pegadamase	Severe combined immunodeficiency disease (SCID)	IM*inj*	8
Pegaspargase	Leukaemia	IM*inj*, IV*inj*	
Peginterferon-alpha 2b	Hepatitis C	SC*inj*	
Peginterferon-a2a	Hepatitis C	SC*inj*	
Pegfilgrastim	Neutropenia	SC*inj*	
Pegvisomant	Acromegaly	SC*inj*	
Pegaptanib	Age-related macular degeneration	IVIT*inj*	
Epoetin beta-methoxy polyethylene glycol	Anaemia associate with Kidney disease	SC*inj*, IV*inj*	
PEG-Certolizumab pegol	Rheumatoid arthritis and Crohn's disease	SC*inj*	
Ziv-aflibercept	Metastatic colorectal cancer	IV*inj*	9
Ocriplasmin	Symptomatic vitreomacular adhesion	IVIT*inj*	
Raxibacumab	Inhalational anthrax	IV*inf*	
Belimumab	Systemic lupus erythematosus	IV*inf*	
Ipilimumab	Unresectable or metastatic melanoma	IV*inf*	
Belatacept	Prophylaxis of organ rejection (kidney transplant	IV*inf*	
Brentuximab vedotin	Hodgkin lymphoma and systemic anaplastic large cell lymphoma	IV*inf*	
Asparaginase Erwiniachryanthemi	Acute lymphoblastic leukaemia	IM*inj*	
Aflibercept	Neovascular age-related macular degeneration, Macular oedema following central retinal vein occlusion (CRVO)	IVIT*inj*	
Velaglucerase alfa	Type 1 Gaucher disease	IV*inf*	
Tesamorelin	Lipodystrophy	SC*inj*	
Tocilizumab	Rheumatoid and systemic juvenile idiopathic arthritis	SC*inj*, IV*inf*	
Collagenase clostridium histolyti-cum	Dupuytren's contracture	IL*inj*	
Alglucosidase alfa	Pompe disease	IV*inf*	
Denosumab	Postmenopausal osteoporosis	SC*inj*	
IncobotulinumtoxinA	Cervical dystonia	IM*inj*	9
Pegloticase	Chronic gout	IVi*inf*	
Insulin	Diabetes mellitus	*P*	7
Captopril	Antihypertensive	*O*	
Enfurvitide	Antiviral	*P*	
Streptokinase	Thromboembolism	*P*	
Oxytocin	Induction of labour	*P*	
Angiotension II antagonist	Lowers blood pressure	IV*inf*	6
Bradykynin	Vasodilation	ID, IV*inj*	
Cholecystokynin (CCK-8 or CCK-32)	Suppress appetite	IVEN*inj*	
β-endorphin	Relieves pain	IVEN*inj*, IV*inj*	
Interferons	Enhance activity of killer cell	IV*inj*, IM*inj*	
Gastrin antagonist	Reduce secretion of gastric acid	IV*inj*	
Pancreatic enzyme	Digestive supplement	O	
Human-growth hormone	Dwarfism	IM*inj*	
Vasopressin	Diabetes insipidus	IV*inj*, IM*inj*	
Risperidone	Schizophrenia	IM*inj*	
Naltrexone	Alcohol and opioid dependence.	IM*inj*, SC*inj*, O	
Leuprolide	Prostate cancer patients	IM*inj*, SC*inj*	
Somatropin	Somatotropin deficiency, Obesity therapies	SC*inj*	
Triptorelin	Prostate cancer	IM*inj*	
Buserelin	Prostate cancer	SC*inj*	
Lanreotide	Acromegaly, Carcinoid Syndrome and Neuroendocrine Carcinoma	IM*inj*, SC*inj*	
Bromocriptine	Acromegaly, Diabetes- Type2, Hyperprolactinaemia, Parkinson's Disease and Tardive Dyskinesia	O, V, IV*inj*	

† Rfr = References; IMInj = Intramuscular injection; IVinj = intravenous injection; SCinj = Subcutaneous injection; IVITinj = Intravitreal injection; IVinf = Intravenous infusion; ILinj = Intralesional injection; P = Parenteral; O = Oral; ID = Intradermal; IVENinj = Intraventricular injection; V = Veginal,

transfer of initial dose towards its targeted site.[10] Therefore, the putative effect of DDS routes on drug bioavailability verifies the initiation and the duration of the pharmacological effect.[11]

Factors affecting the bioavailability of protein and peptide drugs include molecular weight and particle size. Large molecular size and hydrophilic nature of proteins and peptides, act as major factors affecting their passage through cellular membrane, and even limit the paracellular pathway.[12,13] Protein and peptide drugs having smaller molecular weight <50kDa, are easily discharged owing to kidney filtration. Small peptides having hydrophobic amino acids cross the hepatocyte membrane via passive diffusion, and large proteins use the receptor-mediated transport pathway.[14] Proteins having size >1kDa revealed 0.5 to 5% bioavailability. Besides, 1µm particle size easily enters blood circulation after intranasal administration.[9] There is an inverse relation between particle size and dissolution rate. The particle size decreases with the increase in surface area and rate of dissolution. Micronization of drug increases both the dissolution rate and its solubility as digoxin have 100% bioavailability in micronized tablet.[15]

Another factor affecting bioavailability of protein and peptide drugs relates to ionization and pH. Drugs are composed of weak organic acids or bases. These exist in ionized, hydrophilic, unionized, and lipophilic forms in an aqueous environment. The ability of a drug to cross the cell membrane depends upon environmental pH and acid dissociation constant (pKa) of the drug. When given orally, weak-acid drugs are deionized in the stomach, which favours rapid diffusion through gastric mucosa, whereas a weak base drug is ionized in the stomach. For example, aspirin, which is a weak-acid drug, is absorbed more rapidly from the acidic medium of stomach as compared to quinidine, which is a weak-base drug. Mostly drug absorption, either acidic or basic, occurs in the small intestine owing to greater surface area and membrane permeability.[15,16]

In gastrointestinal tract (GIT), change in pH may induce degradation of orally-administered drugs by hydrolysis, oxidation or deamination. In the stomach, proteins and peptides are susceptible to acidic pH. Different barriers regarding oral drug delivery might include enzymatic degradation by pepsin in the stomach, aminopeptidase in brush-border membrane, and pancreatic proteases in the intestine. Pre-systemic peptide and protein degradation due to extensive first-pass metabolism brings low-dose fraction for systemic circulation.[17] Following are the routes of non-parenteral systemic drug delivery:

Oral drug delivery: The typical administration of drug delivery is through oral route. Drugs administered through oral route are absorbed from the stomach and small intestine into the hepatic portal vein, then move directly into the liver, undergoes biotransformation, and, thus, the drug concentration is reduced which is also known as the "First-pass effect". First-pass effect basically reduces the fraction of the drug administered, which enters systemic circulation to be available for therapeutic effect. At the first-pass stage, liver enzyme systems completely destroy the drugs, and they do not enter systemic circulation. For example, glyceryl trinitrate is metabolised completely by the liver and becomes inactive. In addition, some drugs undergo extensive first-pass metabolism. For example, morphine, when orally administered, gives 30% bioavailability, which means that the drug dose given by oral route is higher compared to rectal, IM or IV routes.[18]

Most antihistamines, analgesics, decongestants, antacids are given in solid form. Different drugs, available for oral administration have gone through various challenges before their acceptance as oral drugs. Among these, the initial challenge is to produce a controlled oral release of the drug that gives a relatively firm dose of medicine (almost for eight hours). A tablet after consumption passes through subsequent chemical and mechanical obstruction as it permeates into intestinal mucosa, thus providing a significant challenge in maintaining controlled discharge of the drug. Enzymes, acids and peristaltic conditions can cause the breakdown of the tablet, triggering its release and increase in surface area of peptide drugs. It may increase the transport rate of the drug or poorly disturb the exact assets of the dose.[19] Another challenge is to control drug abuse. For instance, Opioids are medicines used to alleviate pain, but its excessive dose may cause respiratory complications which could be incurable. Despite these challenges, the oral route is the most convenient way of protein absorption.[1]

For protein and peptide drugs various physico-chemical properties are considered for proper delivery. These properties include pH stability, hydrophobicity, ionizing properties and molecular weight along with various barriers, like degradation of enzymes, and changes in pH.[6] At present, two peptide drugs, interferon alpha and human growth hormone are administered orally.[20] Simvastatin, piperine, ibuprofen, amphotericin B are also used for oral drug delivery.[21] Following are some major challenges encompassing optimal release of protein and peptide drug via oral route; widespread hepatic absorption, intestinal tract degradation, greater molecular size and poor permeability. Special techniques, like transformation of proteins, muco-adhesive polymers, enzyme inhibitors or permeation enhancers must be used to improve their

optimal release.[22] Proteins and peptides exhibit poor oral bioavailability due to low permeation across intestinal epithelium, aggregation and denaturation.[9] Orally administered drugs, like indinavir and imatinib, have low bioavailability at about <1% and <10%, respectively. This hurdle was overcome by introducing ionizable groups that escalated the overall molecule solubility up to 60% and 98%.[23]

Buccal drug delivery: Buccal delivery of peptides is considered as a passive absorptive mechanism. Absorption of buccal peptides is greatly affected by its polarity, dissociations, chemical and enzyme stability along with molecular weight. Peptides such as vasopressin, buserelin, insulin and oxytocin, act as feasible drugs, while protirelin is also absorbed by buccal mucosa using hydroxyethyl cellulose.[6] The main advantage of buccal drug delivery over oral delivery is the administration of medication via the buccal mucosa that impedes GIT enzymatic degradation and hepatic first-pass effect. The bioavailability of atipamezole is about 33% for a buccal spray which is far better than <2% oral bioavailability. Furthermore, morphine sulphate represents 30% bioavailability from the bucco-adhesive tablets, and butorphanol bioavailability is 29%, which is less than nasal route delivery but better than sublingual. Testosterone, as an important sex hormone, represents 3.3-fold increase in bioavailability upon buccal delivery route.[24] Proteins and polypeptides improve drug stability, decrease immunogenicity, enhance membrane permeability, lessen bioactivity. However, on the other hand, they also increase GIT toxicity. Mucosal adhesion enhance peptide drugs retention time in GIT, thus, increasing its bioavailability, but it may not improve oral permeability.[25]

Nasal drug delivery: An alternative path for the universal accessibility of drugs restricted to intravenous administration is nasal drug delivery route. The nasal route is ideal due to the huge surface area, high blood flow, evasion of first pass metabolism, and ready convenience.[26]

The nasal route is considered as an efficient route of drug delivery, especially for those drugs which are difficult to inject in crisis treatment, like in pain, and for drugs whose route from nose to brain is considered effective. Nasal administration provides enhanced bioavailability of drugs. The use of bio-adhesive DDS, including liposomes, microspheres and gel, has increased the rate of bioavailability of drugs administered via the nasal route i.e., insulin and other growth hormones.[27] Although the bioavailability of insulin is <1% through the nasal route, it increases up to 46% by using bio-adhesive chitosan gels.[28] The first drug for treatment of influenza was marketed in 2001, but its use was ceased due to some toxicological problems. The use of some drugs for nasal absorption route is considered very effective, like the use of cyclodextrine was initially considered ideal, but later its use was disapproved for humans, but it is still in use for nasal solubilization. Nasal DDS also presents some problems i.e., molecules of high molecular weight have low permeability, so some drugs are not able to assimilate in the body, and, also, nasal delivery causes nasal allergy, nasal congestion and nasal infection.[29]

Drugs absorbed through the nasal passage firstly enter the systemic circulation and then the hepatic circulation, thus, enabling active drugs to lessen histaminic signs in nasal cavity. Low bioavailability of nasal peptides might be due to peptide size and its liability to hydrolytic degradation in the nasal cavity through absorption by passive diffusion. Nasal delivery for synthetic vasopressin, including phenylalanyl-lysine vasopressin and Desmopressin, has been established. In addition, horseradish peroxidase, lypressin, oxytocin and nafarelin acetate have also been advertised as nasal therapeutics.[6]

Pulmonary drug delivery: The diseases which are not cured by oral drugs are treated by pulmonary drug delivery, and have various benefits over transdermal, oral or intranasal substitutes. Insulin (MT 5786) upon pulmonary administration revealed >50% bioavailability in rabbits and 25-75% in humans from the aerosol device. Other examples of absolute bioavailability of drugs include human calcitonin with 17% absolute bioavailability, glucagon with less than 1%, somatostatin <1% and parathyroid hormone with >23% bioavailability.[30-32] For asthma, pulmonary delivery is widely used and its bioavailability may be influenced by physical features of absorbed protein. Morphology, stability, size of particle, and uniformity are the factors employed in preparing drugs for inhalation. Some proteins and peptides therapeutics for lung and systemic delivery may include growth hormones, para-thyroid hormones, albumin, interferons, antitrypsin, leuprolide, and insulin.[33] Pulmonary drug delivery offers a direct way for drug circulation. Aerosol and dry precipitates are employed in pulmonary delivery of peptide or protein therapeutics such as insulin is administered by aerosol and calcitonin is delivered as dry powder.[34,35]

Ocular and transdermal delivery: Some of the drugs for ocular delivery are cyclosporine A, dexamethasone, timolol, flurbiprofen, ketorolac and pilocarpine nitrate with have various pharmaceutical uses.[36,37] Ocular bioavailability varies from 0.07% to 10%. Lipophilic drugs have greater bioavailability than hydrophilic compounds due to their enhanced permeability in cornea. Increasing the corneal contact time is the best way to improve bioavailability.[38,39] Low bioavailability is due to short residence time, tear

production, less absorption, and low corneal permeability.[40] Transdermal delivery involves various drugs such as dapsone, erythromycin, indomethacin, silver sulfadiazine, antimicrobial peptide LL-37 and palmitoyl peptides.[41,42] For molecules with poor bioavailability, feasible non-parenteral routes are administered, such as, transdermal drug delivery route with better absolute bioavailability and short biological half-life. With the help of transdermal route delivery, the bioavailability of glyceryl trinitrate, testosterone, oestradiol increases up to 26%, 8-14% and 10% respectively, which upon oral delivery route is less than <1%.[43-45]

Different factors affect the ocular absorption of peptides such as lacrymal drainage, dilution of tear, and binding of protein. Pharmacodynamic reactions were observed using insulin and glucagon as eye-drop formulations. Skin encompasses aminopeptidases with less enzymatic activity, which increases the bioavailability of transdermal drugs as compared to oral delivery routes. Such transdermal schemes are known for smoking termination, hormone replacement remedy and management of discomfort or discomfort management.[7]

Rectal and vaginal delivery: Rectal delivery of drugs is a novel idea for systemic peptide-based drug delivery where the upper venous system is linked with the portal system, and the lower venous system has direct contact with systemic circulation. Rectum has a stable environment and lower enzymatic activity as compared to GIT. Drugs partially bypass liver, followed by systemic circulation, reducing hepatic first-pass effect. Vaginal permeability is higher for lipophilic steroids (progesterone and oestrone) than hydrophilic steroids (hydrocortisone and testosterone). Lipophilic drugs with lower molecular weight have greater absorption than higher molecular weight drugs.[46,47] Rectal delivery helps hepatic first-pass eradication and decreases protein/peptides proteolytic degradation, thereby improving bioavailability. Insulin absorption from micro enema administered with sodium 5-methoxy salicylate has been studied. Lecithin also extends insulin hypoglycaemic effect due to release of sodium salicylate.[6] Different factors affect rectal route absorption including buffer capacity, or pH of rectum fluid, pressure applied by rectum walls, solubility and particle size of drug. Gels and solutions are employed for peptide delivery, but gels maintain balance between retention time and drug release rate.[48,49] While vaginal drug delivery involves possibility of self-administration, elongating retention periods, and decreasing proteolytic degradation. Vaginal permeability has been affected by serum estrogen levels. This route is helpful for delivery of luteinizing hormone-releasing hormone (LHRH) along with artificial analogues, thus releasing gonadotropins.[6]

Barriers to protein and peptide delivery: The effective delivery of peptide and protein therapeutics is noticed by the ability to cross several barriers offered in the biological locale. These barriers include:

Enzymatic barriers: Various enzymes, like aldehyde dehydrogenases, carboxylesterases, glutathione S-transferases, have been used in drugs' metabolic paths.[50] Some peptides, like insulin, desmopressin and calcitonin, have difficulty in absorption due to proteolytic enzymes. Drug carriers and muco-adhesive systems keep drugs away from enzyme degradation.[51] GIT affects the drug utilization. When peptides cross the stomach, they undergo hydrolysis, thus, losing bioactivity owing to gut pH. In addition, drugs degrade into smaller peptides/amino acids due to proteolytic enzymes, thus, a problem for peptide/protein drug absorption.[25] Enterohepatic circulation (EHC) involves the circulation of various peptide drugs from liver to bile which are reabsorbed into the small intestine and are transported back to the liver for further systemic circulation. Intestinal microflora produces β-glucuronidase that plays a significant role in de-conjugation of glucuronide metabolite of the drug, allowing the availability of parent peptide drug for reabsorption. In addition, cysteine S-conjugate beta-lyase metabolize cysteine conjugates of peptide drug and control the rate of circulation of cysteine.[52-54] Multiple-peak phenomenon is shown by drug in EHC in its plasma-concentration-time profile, hence, represents prolonged half-life elimination. The entry of xenobiotics is inhibited by GIT, which is a significant barrier. Antibiotics block EHC due to suppression of intestinal flora, resulting in reduced deconjugating enzyme levels. The most significant xenobiotics transporters include adenosine triphosphate (ATP), binding cassette (ABC), and the solute carrier (SLC) superfamilies, which are mapped on the apical and baso-lateral membranes of enterocytes, causing enhanced bioavailability of drugs.[52,55] Pancreatic enzymes are also considered major barriers. For colon delivery, poly (lactic-co-glycolic) acid nanoparticles have been used and intestinal discharge was considerably evaded due to the inadequate pH of the environment.[56] Absorption as well as the half-life of peptides is mostly affected by the process of enzymatic degradation. Moreover, more than one enzyme may act upon the single peptide. Protein and peptide drugs do not have the ability to pass through the mucosal material, so mostly the products are formulated in an injectable form. Hence, it is unpleasant regarding patient compliance, tolerability and needs highly trained people for supervision. Thus, significant progress has been made to develop non-invasive delivery of proteins.[57]

Mucus barriers: Mucus has the ability to eradicate outer particles by space-adhesion barriers, preventing pathogens to enter epithelial cells of mucus and limit drug diffusion and absorption, providing mucus bioavailability.[58] Adhesive forces produced by carboxyl group and negatively charged sulfuric acid of oligosaccharides are monitored by hydrophobic parts or mucinous proteins, offering resistance to drugs.[59] Mucus in peyer's patches aids the disruption of nanoparticles by mucosal barrier and duodenal lymphatic tissues, entering blood circulations. A balance among degradation, mucus excretion and sanction in GIT protects the epithelium and regulates food absorption.[60] The passage for protein and peptide drug delivery across the mucosal tissue, involves paracellular and the transcellular pathways. Proteins are the charged molecules, and don't have the ability to pass through the lipophilic membrane easily (transcellular transport). As such, paracellular transport becomes a more predominant mechanism for the absorption of proteins and peptides. Such macromolecules, having size ranging from 600 to 10,000 Da, are much larger than the predictable biological molecules of the drug. Hence, the larger molecules contribute towards the resistance for protein and peptide transport.[57]

Intestinal epithelial barriers: Intestinal epithelial and membranous cells are vital transport cells in GIT. Such epithelial cells have a major role in maintaining its polarity and regulating its permeability. Drugs might be absorbed by cross-cell pathway through passive diffusion, vesicle transport system and carrier-diffusion.[61] Transcellular pathway is a route for drug absorption in which drug crosses the epithelial cell membrane, entering enterocytes, and the other one is paracellular pathway permitting absorption of hydrophilic molecules. Sometimes, the residence time of drugs with the absorbing surface is short, which may hinder the therapeutic effect of drugs. Hence, the short residence time interval of dosage may affect the bioavailability of drugs.

Blood-brain barrier: The blood-brain barrier (BBB) is considered a metabolic/physical barrier restricting passage between blood and neural tissues. It has a vital role in maintaining the stability of brain tissues, and protecting the central nervous system (CNS) from progression of diseases by blood microbes. Inner covering of BBB consists of endothelial cells on brain walls and tight junctions, which obstructs transport of nanoparticles by the paracellular pathway between the inner endothelial cells. In addition to physical barriers, it also has a biochemical barrier including enzymes and various transporters. More resistant cells among the endothelial cells have electrochemical base of BBB.[62] Tight junctions in BBBs are formed by cohesive system, smaller hydrophobic molecules and different cells such as macrophages, monocytes and neutrophils, which might be carried to the brain. The physiological brain environment and exchange between peripheral nervous system are dependent on features of BBB, while morphological BBB structure helps in brain protection. Physiological barriers avoid the transportation of therapeutic agents to the brain. Paracellular and transcellular passages were also employed for proper transfer of therapeutic agents into the CNS.[63] Intranasal drug transport is also important for neurological ailments, where drugs may enter the CNS through the BBB.[56]

Conclusion

The success of the therapeutics is strongly influenced by the differential delivery of targeted antigen, the choice of targeting protein or peptide, and drug-release characteristics of the linker used. As the use of protein and peptide therapeutics is increasing progressively, there is a need to find a proper way for the drug administration. Besides IV, IM, SC drug delivery, there should be an improvement in non-parenteral DDSs so that the drugs might be administered in an appropriate manner. Due to enzymatic and physiochemical barriers, the non-parenteral route is not by far the most successful route for drug administration. So far, specialized DDSs result in limited improvement. Only the oral route proves to be useful. Furthermore, there is a need to focus on advanced systems for the delivery of protein and peptide drugs to compensate the barriers that are linked with protein and peptide drugs.

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