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Lipid-Based Nanocarrier as Bioactive Transporter for Peptide Delivery: A Recent Update

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Abstract

Lipid-based Nanocarriers are becoming popular nowadays because of their potential application in oral drug delivery systems having advantages like strong compatibility, and low toxicity. The bioactive molecules for nanocarrier drug delivery systems play a role in the promising treatment of diseases like urinary tract infection, dental problems, cancer, etc. To overcome the problem i.e., physical, and chemical unstability, various types of nanocarrier delivery systems that stabilize by using approaches of encapsulation technology are introduced. Lipid nanoparticles are stabilized by adding emulsifiers. The main aim of this article is a detailed discussion of different types of colloidal nanocarrier, advantages, disadvantages, different types of barriers to the delivery of protein and peptides, approaches for enhancing oral bioavailability of protein, and peptides. The eudratec pep technology, peptelligence and eligen technology are the newer technology to overcome the problem that arises in the protein and peptide delivery.

Keywords

Nanocarrier, Fabrication technology, Eudratec pep technology, Peptelligence, Eligen technology.

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INTRODUCTION

With the launch of the recombinant human insulin in 1982, the engineered sub-micron system (nanosystem) becomes the irreplaceable component of the pharmaceutical, biotechnological, socio-economical system. Almost 150 billion$ has been spent on this system by 622 companies over 1800 products till 2015.[1–4] Nanocarriers are becoming more popular from decades ago because of the forefront of the potential application in oral drug delivery systems. Oral administration of drugs is widely accepted and used by the patient due to ease of administration, non-invasiveness, self-administration, etc.[5, 6] Epidemiological and clinical investigation proved that bioactive molecules for nanocarrier drug delivery system have end number of advantages, among them their antioxidant activity play key role for the treatment of many diseases like urinary tract infection, dental problems, cancer, etc. Also used for both prophylactic and therapeutic purposes. Now the problem encountered is the physical and chemical instability of the biomolecules.[7–9]Basically instability occurs due to its susceptibility towards hydrolytic degradation, light, etc which in turn leads to the generation of free radical molecules and ultimately hampering in odor and taste of the fortified product.[10–12] Then the introduction of various types of nanocarrier delivery

systems helps in overcoming this problem where it stabilizes by using two approaches of encapsulation technology i.e. microencapsulation and nanoencapsulation respectively. Nanocarrier is the backbone for the delivery of proteins and peptides in the following way:

- Represents particles less than 100 nm.
- Because of the biodegradability wilderness
- Due to ease in Surface modification loading capacity can be increased.
- Due to non-antigenicity
- Makes protein and peptide very stable.
- Allow the products on a comparable scale with other nanosize biomolecules.
- Capability to attach covalently with drugs and ligands.
- It increases the loading capacity of peptides.
- Mask the flavour.
- The physiological barrier is overcome by nanocarriers.
- Problems like low solubility, enzymatic degradation can be solved.
- Nanocarriers allow delivering biotech drugs over various anatomic extremities such as BBB, tight epithelial junction of skin, branching pathways of pulmonary system, etc.
- Due to the leaky constitution, pores ranging from 100-1000nm in diameter, better penetrates tumor.
- It acts at the precise location of the affected body part only.
- It allows preparation to stay in the circulatory system for a longer period which sustains the release of drugs.

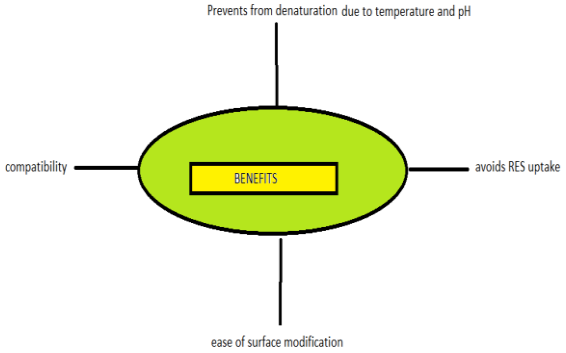

Fig 1

Types of colloidal nanocarriers

It is made up of biodegradable natural or synthetic polymers. It can either be material or a device. It is based on the type of disease we are focusing on the location of the infection, making it compatible with physiological and biological characteristics of body fluids. Different types of nanocarriers are enlisted below:

Lipid nanoparticles- lipid nanoparticles are generally represented by solid lipid nanoparticles (SLNs) also commonly explored areas in peptide delivery relating to nanocarrier. It is taken into consideration because of its natural composition and biocompatibility. It is also considered as first-generation lipid nanocarriers. Solid lipid nanoparticles are nanosized colloidal carrier systems that remain solid at both room and body temperature.[13] It is prepared by the development of O/W nanoemulsion or emulsion at a temperature above the melting point of an oil phase and allowed for subsequent cooling to crystallized lipid droplets.[14,15] It is composed of natural, semisynthetic, and synthetic lipids like triglycerides, waxes, sterols, etc. Here the drug is either dissolved or dispersed in the hydrophobic core of the nanocarrier. Since it contains lipid, it is unstable, so for making stable, emulsifiers are added, and the concentration of emulsion is 0.5-5%.[16]

Properties and advantages of SLNs

- Low cost
- Good release profile
- Basis of large-scale production
- Required to develop evasion system to enhance circulation time which leads to sustained and controlled release.
- Favorable compatibility
- Non-toxic compared to polymeric nanoparticle.
- Effective potent non-viral transfection agent
- Surface modification accounts for high loading capacity
- High tolerance capability due to physiological fluids.
- Mass scale-up production
- It can be delivered by various routes like parenteral, pulmonary, topical, etc.
- The hydrophobic ion-pairing technique is used to increase peptide hydrophobicity.

Disadvantages

- Particle growing, Unpredictable gelation, unexpected dynamics of polymorphism transitions,
- Due to crystalline structure, the incorporation is low.

In the preparation of solid lipid nanoparticle, w/o/w double emulsion is used widely as it is significant in loading of protein and peptide.[17] Peptide release pattern depends upon its composition depicted as.[18–20]

Monoglycerides > Diglycerides > Triglycerides

Components	Release mechanism
Monoglycerides	Lipase mediated degradation
Diglycerides	Lipolysis mediated and peptide diffusion
Triglycerides	Simple diffusion

Table 1

Cationization in peptide delivery is used to enhance entrapment efficiency because of ionic interaction with anionic lipids like the incorporation of anionic lipid lecithin into SLNs leads to the continuous release of VEGF for over 45 days. While in the case of insulin, initially it was positively charged in an acidic medium to promote entrapment in SC micelles and once it reached physiological pH, a charge of insulin was inverted. Finally, the repulsion between the drug and bile salts broke down the system, thus burst drug release occurred. [1]

A clear-cut knowledge of the physical properties and chemistry of lipids is a prerequisite for the proper formulation. Some of the factors considered for the selection of liquids include purity and chemical stability, solvent capacity, water miscibility, digestibility, and fate of digested products[1]**,** electrical characteristics, polarities, of bioactive proteins because it affects the loading, retention, stability, and release of colloidal system and safety and regulatory profile. Proteins and peptides are very often prone to denaturation, aggregation, or hydrolysis.[21] **Xu yining** et al studied that lyso-endosomal degradation was significant. So, for overcoming this problem they revealed that ins HA2-O-SLNS were easily escape loaded insulin from lyso-endosomal degradation. HA2 was used as endosomal escape agent which promotes intracellular transport to a great extent. It was denoted that faster release was obtained when HA2 peptide was used in HA2-O-SLNS rather than in ins HA2-W-SLNS.[22] **Alsulays et al** studied penetrating stereochemistry where they proved that DP-INS-SLNs were most stable due to the protective nature of DP resulting in the increased half-life and restrict enzymatic degradation as compared with other SLNs. Penetrating stereochemistry significantly impacted oral BA of INS-SLNs, which are promising carriers for oral INS administration.[23] **Fangueiro J. F et al** prepared placebo-SLNs(insulin-free) and insulin-SLNs and indicated that components used were tolerable and suitable for oral delivery[24]. **Sinem Yaprak Karavana** studied that the SLN-incorporated gel would be beneficial for increasing the retention time and penetration (i.e., the enhanced permeability and retention effect) of the SLNs at the application area promoting a rapid decrease in ulcer size with the application of the ideal gel containing CsA-loaded SLNs.[25] **Haibing He** et al found that a new structure of VB12-GCSLN had higher insulin encapsulation efficiency (EE) of 55.9%, a lower burst release of less than 10% in the first 2 h which signifies the VB12-GCSLN developed in this study might be employed as a potential approach to promoting the efficiency for oral delivery of protein drugs.[26] It also has been concluded that the peptide grafted nanoparticles (A-SLN) showed increased cytotoxicity, enhanced cellular internalization, and prominent apoptosis than that of unconjugated nanoparticles against U87MG human glioblastoma and GL261 mouse glioma cells i.e., survival time was increased significantly from 24 days to 39 days.[27] **Vincent Jannin** et al suggested that the high affinity of pancreatic lipases makes lipid nanoparticles makes a versatile drug delivery system for poorly water-soluble drugs which get absorbed from the duodenum.[28] **Tahereh Daraa** *et al* prepared the first EPO-SLN formulation using Box-Behnken design indicated 2500 U EPO loaded SLN showed great capacity in elevating RBC, hemoglobin, and hematocrit level when compared to 5000 U EPO solution.[29]

NLC

Nanocarriers are in nanoscale structured lipoidal carrier diameters ranging from 10-1000nm.[30,31] It is the modified or newer generation of solid lipid nanoparticles that remain a solid matrix of lipids at both body and room temperature. It came into existence to overcome various limitations possessed by solid lipid nanoparticles.[32,33] It is a system of low viscosity aqueous dispersion.[34] The nanostructured lipid carriers provide a better payload for many drugs

along with restriction from drug expulsion during storage and low water content in nanostructured lipid dispersive system are shown in the Table 2. [31,35]

S.No.	Limitations	Cause	Solution
1.	Low payload/loading capacity	Formation of lipid crystal	Make use of mixed lipid liquids with solids lipids along with various triglycerides
2.	Drug expulsion during storage	Formation of highly ordered crystalline and β-modification	Make use of lipid blends
3.	High water content	Irregular intracellular compartment	By using lipid conjugation
4.	Physical instability	Aggregation and gelling	Make use of freeze-drying process and addition of preservative

Table 2

The NLCs contain both solid lipids and liquid lipids in the lipidic phase at both room and ambient temperature.

Types of NLCs

Depending upon the composition of a blend of lipids, the content of lipids and fabrication technology, NLCs can be divided into three classes. They are as shown in the Table 3:

Type of Class	Name of class	Description	Advantage
I	Imperfect crystal type (imperfectly structured solid matrix)	The blending of spatially different lipids like glycerides (fatty acids) creating imperfections in order of crystallinity	Payload is high
II	Amorphous type (structureless solid amorphous matrix)	Formed by addition of special liquid lipids like hydroxy octacosanyl hydroxy stearate or iso-propyl myristate with the solid lipid.	Prevents drug expulsion occurring from β-modification during storage and lesser payload from imperfect type
III	Multiple type (multiple oil in fat in water (O/F/W) carrier)	Provided with enormous nanosized liquid oils throughout the lipid matrix	Drug solubility tends to increase

Table 3

Fabrication technology in NLCs

It has always been a better option for the delivery of drugs through nanostructure drug delivery system.

Type/Techniques	Method and properties of preparation	Usefulness	Limitations	References
High-pressure homogenization (HPH)	High pressure (100-200) is used to melt the combination of lipids, aqueous surfactants at the same temperature. Generally, the lipid content in this section is 5-10%. Water-soluble drug is added to the melted lipid compound.	Basis for cost effective and large-scale production *Reliable and powerful technique for lipid drug conjugation, SLNs, parenteral emulsions, etc*	Absolute negligence of drug disclosure to high temperature is not feasible.	[36–38]

High-shear homogenization		Short scale-up time It can be used for both hydrophilic and lipophilic drugs. *Less amount of emulsifying agent is used when compared to microemulsion technique.* Manufacturing in both lab-scale and industrial scale is possible.	Not applicable for the processing of large amounts of multiple samples side by side because swapping out and cleaning between runs is necessary.	[39,40]
Hot homogenization	The drug along with lipid are dispersed in an aqueous surfactant by using a high shear device where pre-emulsion is formed and homogenized by utilizing a piston gap homogenizer and finally formed nanoemulsion is cool down at room temperature followed by recrystallization leading it to the formation of nanoparticles.	*Widely used for large scale production*	Degradation of drugs at high temperature. *Drug loss because of partitioning of drug into aqueous surfactant phase* Thermolabile drugs can't be formulated by this method.	[38]
Cold homogenization	Here, drug(solid) lipid molten is used where it follows the first step is as same as hot HPH followed by rapid cooling using liquid nitrogen or dry ice resulting into the solidification and distribution of drug in lipid matrix.	Makes quite easy for preparation of thermolabile drugs. *Minimizes the use of organic solvent like chloroform, acetone, etc.* Large molecules with greater polydispersity are found with cold homogenization technique.	Huge amount of energy is required. Polydisperse distribution Biomolecule damage	
Phase inversion	For this purpose, emulsifiers are added. Since it is formed in two steps i.e., w/o is formed as a result of the heating aqueous phase and lipidic phase separately just above the melting point.	The organic solvent can be avoided. *In the formulation of thermolabile drugs.*	Heavy and large enough to carry it out	[41–43]

	Then add dropwise aqueous phase to lipidic phase at temperature. Emulsifier leads phase inversion process from w/o to o/w emulsion. The temperature cycles like 85-60-85^{0}C. The HLB value of surfactants are high at low temperature because hydrophilic groups are extensively hydrated.			
Solvent emulsification-evaporation technique	Lipids are incorporated in a water-immiscible organic solvent like chloroform followed by an emulsification process in an aqueous phase containing surfactants under continuous stirring. Then organic solvent gets evaporated leaving lipid precipitate. Chloroform, cyclohexane, toluene like organic solvents is mainly used.	Suited for thermolabile drugs	The organic solvent may present in formulation hence ultrafiltration and ultra evaporation is required	44,45
Solvent emulsification-diffusion technique	Here, both organic solvent (partially immiscible) and water are mixed to provide thermodynamic equilibrium. The transient oil-in-water emulsion is passed into water under continuous stirring, which leads to the solidification of dispersed phase forming lipid nanoparticles due to diffusion of the organic solvent. Partially immiscible organic solvents used for this method are methyl acetate, ethyl acetate, isopropyl acetate, benzyl alcohol, and butyl lactate.	Water immiscible solvents are used to dissolve lipids	Lyophilization or ultrafiltration is required	46
Supercritical fluid technology	It uses the gas saturated solution for the preparation. It uses supercritical fluid-like	Prepared in the form of dry powder rather than suspension		47,48

	supercritical CO_2. This method has high solvent extraction efficiency when compared to diffusion, dilution, and evaporation.			
Microemulsion techniques	Shock cooling and probe sonicator are used for the preparation of nano emulsion. This technique involves diluting a microemulsion in a cold aqueous solution forming nano emulsion.	Industrial scale-up is possible. Minimize the use of co-surfactant and surfactant	Low nanoparticle concentration	49
Membrane contractor technique	Here, lipidic phase is pressed through the small pores of membrane forming small droplets followed by cooling at room temperatures, finally recrystallizes to form lipid nanoparticles. Here particle size can be maintained by regulating lipid flux through membranes.	Simple and cost-effective method		50,51

Table 4

Different types of barrier/ hindrance factors for the delivery of protein and peptides

The prime function of the gastrointestinal tract are digestion and absorption and is considered as first line of defense against various pathogens and toxins. Oral delivery of protein and peptides are very problematic because of presence of various factors like luminal enzymes, mucosal surface, and biochemical factors. The different types of barriers are enlisted and explained below:

- **Luminal barrier/ enzymatic barrier:** It is composed of gastric fluid (HCL, NaCl, KCl) and a different type of enzymes (pepsin, gastric lipase). So, we can say that the composition of both the acidic conditions and enzymes synergistically disrupt the nanocarrier or may inactivate the encapsulated drug. If we move through respective part of GIT after stomach, we find that pH is increasing where content of various enzymes like trypsin, chymotrypsin is very low. These enzymes are responsible for the degradation of protein in a fragment for proper absorption. Low content plays important part in creating hindrance factor for absorption of protein and peptides. Luminal enzymes are responsible for forming enzymatic barrier which takes place by catabolic enzymatic activity at brush border membranes.[49] Hence, a novel approach is required for the delivery of proteins and peptides.
- **Mucosal barrier:** Due to viscoelastic and dynamic properties of mucous it is also said as a complex of hydrodynamic gel. It is composed of carbohydrates, salts, protein, bacteria, antibodies, cell debris, etc.[50] The main component of mucous layer is mucin and is secreted by goblet cells of the epithelial membrane. The exposed epithelial surface of mucous layer helps to protect from pathogens and foreign particles by entrapping and detoxifying them.[50, 51] The lubricating function makes peptides a less residence time towards mucosal layer.[52] The role of mucous in stomach and intestine are to protect from acids and bacteria respectively.[53] Nevertheless mucous also helps in reducing mechanical stress of digestion. A thickness of mucous layer varies throughout the GIT tract depended upon the balance between the secretion rate and opposing force of erosion by mechanical stress and luminal

proteases.[54] The mucous layer is divided into two parts i.e., loosely packed layer and firm layer. Firm layer is made up of glycocalyx and is bonded to surface of epithelium. While a loosely packed layer made up of fibrous content which can be easily removed by shearing.[51] The hydrophobic nanocarrier and hydrophilic layer of intestinal epithelial tight junction makes a drug to release in GIT which leads to low oral bioavailability.

Typically looking at the size of mucous it will not create any hindrance factor or blocked sterically by mucin mesh to a nanocarrier. The presence of sialic acid and sulphonic acid makes mucous layer negatively charged but negatively uncharged nanocarrier can move easily across mucous layer.

- **Epithelial cell barrier-** It is divided into two parts i.e., transcellular epithelial barrier and paracellular epithelial barrier. Tight junction at apical part of cells regulate paracellular transport and modification is also limited when compared with transcellular transport. Transcellular transport is mediated by cell transcytosis and intracellular transfusion. One of the recent studies suggested that the rod shaped (250-400nm) polystyrene particles have higher cellular uptake than spheres whereas other study suggested that positively charged particles has higher cellular uptake by endocytosis than negatively charged particles. Negative charged particles are capable changing zeta potential thus making it easier to cross mucosal barrier.[55]
- **Biochemical barrier:** Biochemical degradation initiates from stomach due to instability in acidic environment, luminal microorganisms, or metabolism by digestive enzymes. Bacteria located at colon secrete enzymes that are capable of deglucouronidation, decarboxylation, amide hydrolysis, reduction of double bond, and dihydroxylation reaction. Proteolysis starts from stomach and stagnant throughout the intestine.[55] Pancreatic proteases like endopeptidase, trypsin, chymotrypsin, elastase, and exopeptidase.

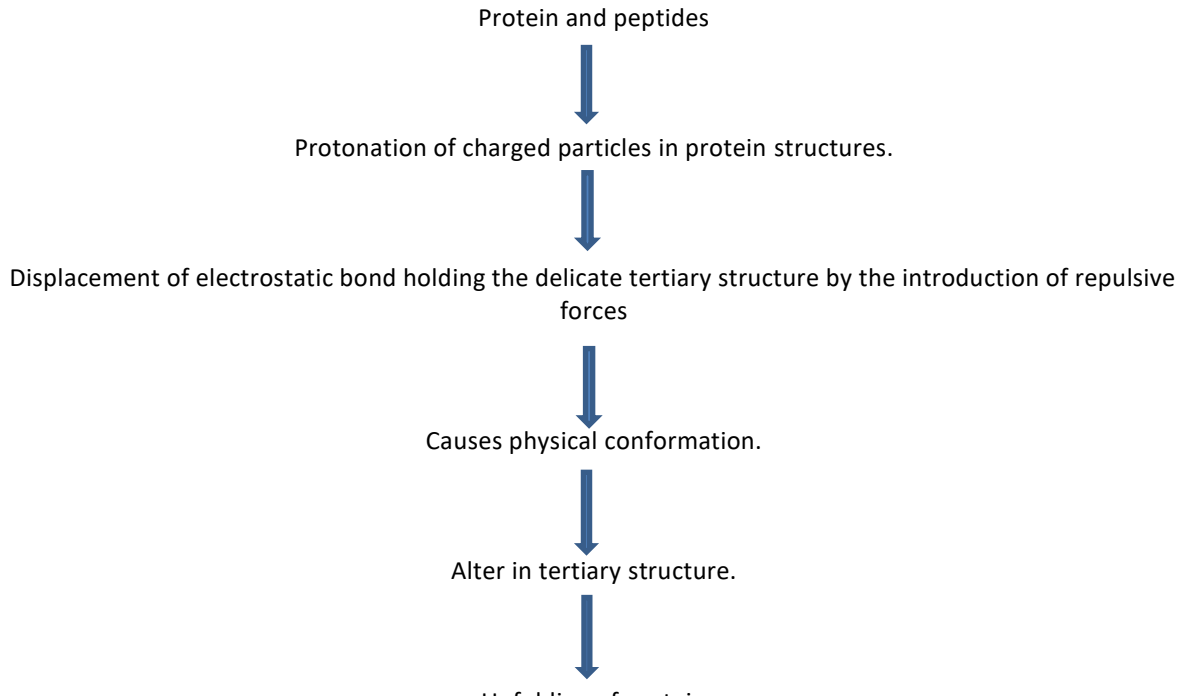

Fig 2: Mechanism of biochemical degradation

For example- pepsinogen is secreted by chief cells which converted to pepsin under the influence of HCl having low PH where activation is less. As it moves towards basic PH more activation occurs which causes cleavage of peptides followed by release of di and tripeptides resulting into the loss of pharmacological response

Approaches for enhancing oral bioavailability of protein and peptide:

Absorption enhancer- Absorption enhancer temporarily or reversibly disrupt the intestinal barrier where it can cause minimum damage to the cell and tissue. However acute epithelial damage can be ignored. The selection of absorption enhancer is a headache for formulation scientist as it depends upon physiochemical characteristics, regional difference, and nature of vehicle. Protein and

peptides are high molecular weight component thus making it difficult for disruption through transcellular and paracellular transport. Several types of absorption enhancer are there, some of them are surfactants, detergents, bile acids, long alkyl chain inhibitor, calcium chelating agents, etc. The other type of absorption enhancers is zonula occulated toxin and peptide carrier. The different type of mechanism of absorption enhancer are changing the membrane fluidity, decreasing mucous, viscosity and facilitating absorption through membrane disruption. Till now, more than 250 absorption enhancers are investigated and may use in preclinical intestinal delivery models. Chitosan and polyacrylic acid are devoid of toxic adverse effect. The widely used absorption enhancer is sodium caprate due to its food additive usage. Calcium chelators will decrease calcium disrupting actin filament followed by modifying adherent junction thereby reducing adhesion. Chitosan relies on charge density along with structural features.[56]

Permeation enhancer- One of the novelistic widely accepted components used for improvement of oral bioavailability of protein and peptides. So, for this alteration in the characteristics of absorptive epithelium are very much important which facilitate both transcellular and paracellular absorption by increasing permeability of plasma membrane and by opening tight junction respectively. Here calcium chelates tends to decrease the tension between attached layer of tight junction by depletion of calcium. It is believed that paracellular pathway modulation is safer than the transcellular pathway modulation. Ideal characteristics include non-toxic, non-irritant, non-allergenic, pharmacologically, and chemically inert. Efficiency is quite variant in different region of stomach due to morphology of cells, enzyme content and membrane thickness. Permeation enhancers increase oral absorption by coadministration of suitable amphiphilic low molecular compound. For avoidance of non-specific absorption, it subjected for local delivery only like hydrogel, intestinal patches, etc.

Agents	Mechanism	Examples	References
Surfactants	Disrupt intestinal membrane and increase transcellular permeability	Sodium lauryl sulphate, polysorbate, TWEEN 80	Anil Kumar et al. (2011); Xia and Onyuksel (2000)
Bile salts	Decrease mucous viscosity & peptidase activity	Sodium glycolate, sodium deoxyglycolate	Maher and Brayden (2012); Sakai et al. (1997)
Fatty acids	Increase intracellular calcium ions tensions that cause contraction of junction associated with filaments	Sodium caprate, acryl carnites, oleic acid	Anil Kumar et al. (2011); Park *et al*. (2011)
Chelating agents	Opening tight junction & maintain structural features of intercellular space	EDTA, citric acid, salicylates	Park et al. (2011); Thanou et al. (2001)
Chitosan and derivatives	Reduce tension of tight junction integrity	N-trimethyl chitosan chloride	Dodane and Vilivalam (1998); Maher and Brayden (2012)
Other enhancers	Several other mechanisms	Zonula occludens toxin, PCP-cycteine	Anil Kumar et al. (2011); Maher and Brayden (2012)

Table 5

Some of the factors influencing efficiency of permeation enhancer are type of protein and peptides and ability to cross intestinal membrane, intrinsic nature of permeation enhancer, the delivery system and rate of release of enhancer.

Prodrugs - Prodrugs are inactivated form of drug produced by chemical modification which get activated inside the body. The prime goal of this modification is for target release, to decrease metabolism or side effect. Due to the lack of methodology for synthesis and poor stability during synthesis limits the application of prodrugs. The process called bio reversible cyclization approach are expected to improve oral absorption of opioid

peptide. Chemical modifications of amino acids like lysine and cysteine do not use for sustained release but expected to decrease side effect and improve stability. Along with this immunogenicity also decreases. Kim *et al*. found that benzepril prodrug showed uptake rate of more lipophilic drug were two times greater than parent drug.[55]

Enzyme inhibitors approach - A hurdle to achieve a good oral bioavailability is due to luminal breakdown of drugs in presence of endo and exo-peptidases such as trypsin, peptidase, etc. This approach works by inhibiting the enzyme functionality and promoting the intestinal absorption. It was observed that the combinatorial use of absorption enhancers and enzyme inhibitors increased the oral bioavailability of protein and peptides. Some of the enzyme inhibitors are mesylate, amastatin, bestatin, boroleucine, puromycin. Lee and Amidon observed that when the insulin was administered with enzyme inhibitor amastatin then the hypoglycaemic effect was increased by 22 times.[56]

Newer technologies used in the protein and peptide delivery.

Eudratec pep technology: Evonik industries introduced this technology. This technique uses capsule as dosage form in place of injection to make it more patient compliance. This technology will help to reduce the problem of solubility and permeability of proteins. This technology provides the formulation in microparticles or mini pellets. By this technology, it was observed that there was increase by seven-fold of relative bioavailability.

Peptelligence: This innovative oral drug technology was developed by Enteris Biopahrma for peptides hence this technology is called peptelligence. This method used BCS-II, III and IV class of drugs. This technology was introduced to overcome the problem of solubility and permeability of protein and peptides.

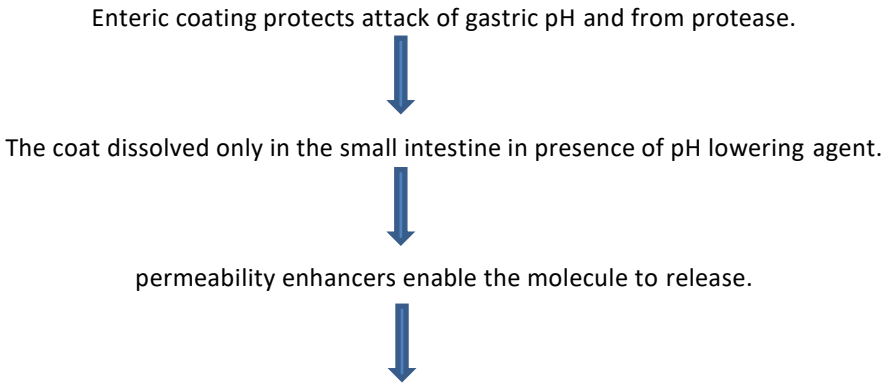

Fig 3: Mechanism of oral delivery

Eligen technology: This technology was launched by the 'EMIAPHERE TECHNOLOGIES'. In this technology the chemical form and biological activity remains unmodified. This technology is extensively used for macromolecules and oligonucleotides increasing bioavailability significantly. It uses carriers for delivery of drugs. It also helps to replace injectables.

PRODUCT NAME	NAME OF COMPANY	COUNTRY OF ORIGIN	BIOPHARMACEUTICAL
Eligen (Vitamin B12 and Rybelsus (Oral Semaglutide)	Emisphere Technologies	Denmark	Calcitonin, insulin, growth hormone, parathyroid hormone, heparin
ORMD-801	Oramed Company	USA	Insulin
'IN-105'	Nobex and Biocon	India	Insulin
Octreolin	Chiasma	Israel	Insulin
AL-401	Eli-Lily	USA	Insulin
Oral-Lyn	Generex Biotech	Canada	Insulin, macrotonin
Orasome	Endorex Corporation	UK	
BioOral™	BioSante Pharmaceuticals	Canada	Insulin and vaccines
Sandimmune	Novartis	USA	

Table 6

CONCLUSION

The several enzymes and mechanism which can destroy the protein and peptides converting it into respective amino acids resulting in poor bioavailability. Previously, many attempts have been done to overcome the problem of solubility and permeability like absorption enhancers, enzyme inhibitors approach etc but due to inbuilt toxicities it has not been used. Similarly, lipid-based carriers were begun to use but this strategy was also suffered from low entrapment efficiency and low oral bioavailability. In recent past several technologies were used but selectively Eligen, Eudrateh pep and peptelligence are showing promising in protein and peptide delivery.

FUTURE PERSPECTIVE

Presently, several technologies are evolving like lipid-based nanoparticles, solid lipid nanoparticles, polymerosomes to deliver the protein and peptides. Newer Techsystems's like PEGylation, CPP, mucoadhesive polymeric system are found to be promising for site specific delivery of protein and peptides. Scientists are doing great work in the field of drug delivery to develop a non-invasive technique for drug delivery which is safer and economical.

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