



## Carrier-Based Systems as Strategies for Oral Delivery of Therapeutic Peptides and Proteins: A Mini-Review

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1 **Carrier-Based Systems as Strategies for Oral Delivery of Therapeutic Peptides and**  
2 **Proteins: a mini-review**

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18 ,

## 1 **Abstract**

2 Peptides and proteins play an essential role in biological systems and the human body.  
3 Deficiency or dysfunction of peptides and proteins such as insulin can lead to various illnesses.  
4 The therapeutic use of peptides and proteins in some illnesses such as diabetes, cardiovascular  
5 disease, autoimmunity, and cancer, among others, is highly considered. Peptides and proteins  
6 have large molecular structures and are generally hydrophilic, and maintaining their spatial  
7 composition or tertiary configurations are necessary for their pharmacological activities.  
8 Maintaining the stability of the protein structure and composition is therefore very important  
9 and necessary to maintain functionality. There are different routes for peptides and proteins  
10 administration such as injection (subcutaneous, intravenous, and intramuscular), oral, nasal,  
11 pulmonary, rectal, and ocular routes. The oral administration route is better accepted by the  
12 patient due to safety and ease of use. However, oral administration often is unsuitable because  
13 of the physicochemical properties and macromolecular structure of proteins and the presence  
14 of gastrointestinal (GI) enzymes under an acidic environment within the stomach. Proteins and  
15 peptides undergo enzymatic degradation, tertiary structural alteration, and low absorption. This  
16 necessitates the need to use alternative oral drug delivery systems for peptides and proteins that  
17 maintain their overall structure and enhances their absorption and bioavailability. In this article,  
18 we review carrier-based oral drug delivery systems that were suitable for peptides and proteins.

19 **Keywords:** Peptides and proteins; Oral delivery; Carrier-based; Bioavailability

## 1 **1. Introduction**

2 Peptides and proteins have many functions, including acting as receptors, functioning as  
3 transporters, controlling gene expression, and facilitating intracellular and extracellular  
4 reactions, all of which play broad and varied roles in living organisms (Doostmohammadi et  
5 al. 2019; Leader et al. 2008). They are generally proposed as significant contributors to the  
6 production of new therapeutic agents for several human diseases such as diabetes,  
7 cardiovascular disorders, autoimmunity diseases, cancers, among many others (Liu et al. 2018;  
8 Tan et al. 2010). Recombinant peptides and proteins, therapeutic synthetic peptides, and over  
9 1000 proteins and peptides have been frequently used therapeutically and in clinical trials  
10 (Leader et al. 2008). Some biopharmaceuticals, including recombinant therapeutic proteins,  
11 monoclonal and polyclonal antibodies, enzymes, and peptides, were reported among the top 10  
12 pharmaceutical products market (Sengupta and Kulkarni 2013). At present, the peptides and  
13 proteins-based drug market are estimated to be worth >\$40 billion annually, representing about  
14 ten percent of the ethical pharmaceutical market. This sales volume has been steadily  
15 increasing faster than other pharmaceutical products, and success rates are now twice that of  
16 small molecule drugs available for the marketing of biologics (Sachdeva 2017). There are many  
17 administration routes for peptides and proteins based drugs, and due to higher safety and better  
18 compliance, significant attention has been devoted to developing the oral administration route  
19 (Liu et al. 2018). However, peptides and proteins face mounting challenges during oral delivery  
20 as they are hydrophilic substances that cannot transfer through the lipophilic cell membrane.  
21 They also are macromolecules that typically have a molecular size > 500 Da, minimizing their  
22 paracellular transmission across tight junctions. Besides, their absorption rate and half-life in  
23 the body is severely reduced in the GI tract due to enzymatic degradation and denaturation in  
24 the highly acidic environment. This makes it challenging to deliver them through oral

1 administration and creates the need to use some novel delivery system (Liu et al. 2018; Mahajan  
2 et al. 2014).

3 A successful peptides and protein delivery system should be able to preserve the protein  
4 activity at the highest level and have characteristics such as high entrapment and drug loading  
5 capacity, good stability, and constitutes a simple and repeatable preparation process (Zhu et al.  
6 2016). Some carrier-based delivery systems such as Nanoparticle, Nanoemulsion, and Lipid  
7 bilayer vesicles have been developed recently. In this review, we focus on several proteins and  
8 peptides suitable oral delivery systems and strategies.

## 9 **2. Therapeutic peptides and proteins**

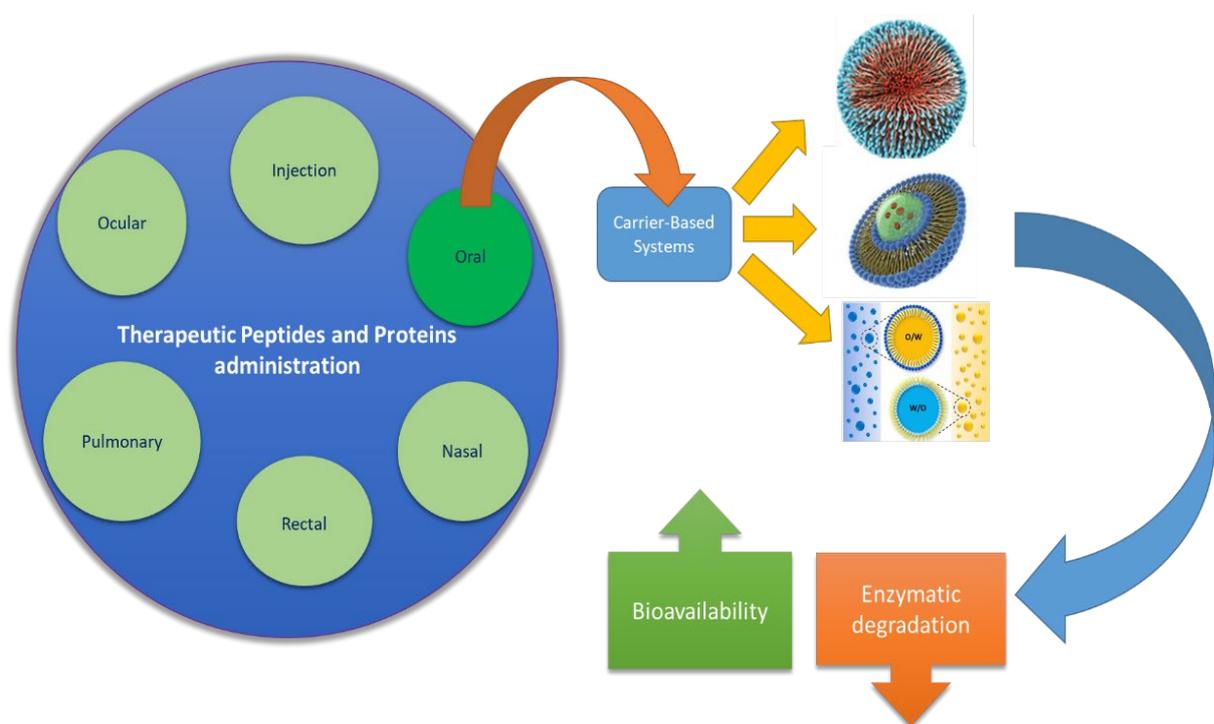
10 Peptides and proteins affect many biological processes, functioning at specific sites as  
11 endocrine or paracrine signals and others as neurotransmitters or growth factors. They are very  
12 specific in action compared to smaller molecules when used as a potential drug (Uhlig et al.  
13 2014). Some peptides and proteins have a pharmacological effect and are used as a drug in the  
14 treatment of some diseases such as cancer, cardiovascular disease, diabetes, multiple sclerosis,  
15 and rheumatoid arthritis (Burmester and Pope 2017; Ciplea et al. 2020; Kurrikoff et al. 2019;  
16 Recio et al. 2017; Sanchez et al. 2016; Shen et al. 2019). They also have antioxidant,  
17 antimicrobial, and anti-inflammatory effects (Cicero et al. 2017). The approval rate of protein  
18 and peptide related drugs has increased substantially since the approval of recombinant human  
19 insulin (Humulin®) in 1982 (Walsh 2000). In 2014, the total number of approved  
20 biopharmaceutical products in the United States and the European Union grew by 246, and  
21 global sales of biopharmaceutical medicines reached \$445 billion in 2019 (Sengupta and  
22 Kulkarni 2013). However, some challenges still exist in peptides and proteins administration,  
23 including lower stability of protein-based drug product, degradation and aggregation of  
24 proteins, low absorption and bioavailability, degradation by enzyme and acid in GI track, and  
25 short half-life, which makes it necessary to repeat administrations to achieve the desired effects

1 (Ibraheem et al. 2014; Wang and Ohtake 2019). Some methods and delivery systems have been  
2 developed to optimize the physicochemical properties of proteins, protect them and deliver  
3 them to their targets within the biological systems (Ibraheem et al. 2014).

### 4 **3. Common peptides and proteins delivery routes**

5 Therapeutic peptides and proteins were typically delivered by different administration routes  
6 that showed in figure 1, such as subcutaneous, intravenous, and intramuscular injections, oral,  
7 nasal, pulmonary, rectal, and ocular routes (Gedawy et al. 2018; Ibraheem et al. 2014).  
8 Administration of peptides and protein by injection routes can often cause some problems like  
9 pain. Also, therapeutic peptides and proteins are quickly eliminated from the blood flow, which  
10 makes it necessary to repeated doses of drugs, thus poorly tolerated by some patients (Allahyari  
11 and Javadzadeh 2019; Cacciatore et al. 2016; Ibraheem et al. 2014). For patients, injection  
12 routes are painful, and they are often costly and can cause harmful and unwanted adverse  
13 effects. As a result, studies have concentrated their attention on developing more effective,  
14 safer, and simpler alternative routes for their delivery, leading to the development of non-  
15 invasive protein drug delivery systems (Allahyari and Javadzadeh 2019; Ibraheem et al. 2014;  
16 Zaric et al. 2019). For both local and systemic effects, nasal peptides and protein delivery can  
17 be used. However, it is usually limited because of the physical barrier of the nasal epithelium,  
18 rapid mucociliary clearance, and a limited number of drugs administered via this route (Chen  
19 et al. 2018; Wei et al. 2020). The rectal route can also be used for local and systemic therapy  
20 but is still limited because of some disadvantages such as low peptides and protein absorption  
21 through the rectal epithelium and overall low bioavailability (Ibraheem et al. 2014). There are  
22 many benefits to the ocular route of protein delivery as it is simpler and quicker than  
23 conventional injection routes. The ocular administration of protein drugs protects them by  
24 avoiding the first-pass metabolism. First-pass metabolism is one cause of low bioavailability

1 of peptides and proteins when administered by the oral route (Allahyari and Javadzadeh 2019;  
 2 Cao et al. 2019; Gedawy et al. 2018; Ibraheem et al. 2014; Mandal et al. 2018). However, some  
 3 reasons limit ocular peptides and protein administration, including poor bioavailability due to  
 4 low permeability of peptides and protein through eye membrane and enzymes in the ocular  
 5 tissue. The ocular route, therefore, is not the optimal route for systemic peptides and protein  
 6 delivery (Allahyari and Javadzadeh 2019; Mandal et al. 2018). Although oral bioavailability of  
 7 protein drugs is limited, the oral administration of protein remains an interesting and attractive  
 8 alternative to conventional parenteral protein delivery, as it is a painless and much easier  
 9 administration route (Allahyari and Javadzadeh 2019; Cao et al. 2019; Gedawy et al. 2018).  
 10 The design of oral delivery system, which can protect the peptides and proteins, improving  
 11 their absorption and bioavailability without interfering or interacting with its biological  
 12 activity, has become attractive and impotent in protein-based delivery systems strategy.



13 Figure 1. Therapeutic peptides and proteins administration routes and schematically carrier-  
 14 based system that used in oral delivery.

#### 1    **4. Oral protein delivery system**

2    The oral route has attracted the most attention among the different administration routes due to  
3    its specific benefits, including controllable delivery, ease of use, feasibility for solid product,  
4    and better patient compliance (Cao et al. 2019; Liu et al. 2018). Protein stability is also one of  
5    the significant challenges facing a product's successful entry into the oral delivery systems  
6    market. The drug delivery system that protects peptides and protein against intestinal  
7    degradation and can increase intestinal permeability is valuable to enhance their oral  
8    bioavailability and overall activity (Rao et al. 2008). To enhance the stability and  
9    bioavailability of therapeutic peptides and proteins, many studies have focused on the use of  
10   carrier-based delivery systems such as Nanoparticles, Nanoemulsion and Lipid bilayer vesicles  
11   that schematically showed in figure 1. (Al-Remawi et al. 2017; Cao et al. 2019; Gedawy et al.  
12   2018; Lee et al. 2019; Liu et al. 2018; Shalaby and El-Refaie 2018).

#### 13   **5. Nanoparticle carrier-based delivery system**

14   The main objectives in such a system often are to monitor particle size and surface properties  
15   in the design of nanoparticles as a delivery system (Jahanshahi et al. 2005). To achieve the site-  
16   specific action of the drug at the therapeutically optimal rate, the release kinetics of the drug,  
17   and dose regimens are critical (Soppimath et al. 2001).

18   Some advantages of using nanoparticles as a method for drug delivery are:

- 19        ✓ Surface morphology, size and properties of nanoparticles can be easily manipulated to  
20            obtain both active and passive compounds targeting the administration routes.
- 21        ✓ Nanoparticles can control drug's release during transport and at the target of the drug,  
22            altering the delivery of the drug by the organ and subsequent clearance of the drug to  
23            improve its therapeutic effectiveness and minimize any adverse effects.

1        ✓ The drug delivery system may be used for several administration routes, including  
2            oral, parenteral, nasal, and intraocular. (Mohanraj and Chen 2006).

3 Drug delivery efficiency is directly related to particle size because particle size can increase  
4 bioavailability and allow more effective direct intracellular delivery (Galindo-Rodriguez et al.  
5 2005). Some studies have found that the amount of nanoparticles crossing the intestinal  
6 epithelium is greater than the number of microspheres and that the transport includes not only  
7 epithelial M cells but also normal enterocytes (Jung et al. 2000). Nanoparticles allow peptides  
8 and protein drugs to cross through the cell membrane, bind, and encapsulate within a matrix  
9 that protects them against enzymatic and hydrolytic destruction (Mohanraj and Chen 2006).

10 Tian et al. (2018), developed a core-shell nanoparticle vehicle as oral insulin delivery that  
11 combines the ability to penetrate mucus, enhanced gastrointestinal retention and transepithelial  
12 transport properties to improve bioavailability. Chitosan modified with N-(2-hydroxy)-propyl-  
13 3-trimethylammonium chloride was used to prepare nanoparticles due to its positive charge  
14 structure of the quaternary amine groups, independent of environmental conditions. The  
15 surface of nanoparticles was coated with polyanionic thiolated hyaluronic acid. The average  
16 size was 75 to 200 nm and the polydispersity index (PDI) varied from 0.23 to 0.40. Cumulative  
17 drug release from modified nanoparticles at pH 7.4 by 24 h was 74.2%. This strategy showed  
18 improved intestinal retention, increased ability to mucus penetration, and transepithelial  
19 transportation (Tian et al. 2018). Xu et al. (2018) used solid lipid nanoparticles for the oral  
20 delivery of insulin. Nanoparticles consisted of a solid-lipid shell and an aqueous core loaded  
21 with hemagglutinin-2 peptide and insulin, respectively. Size, PDI, and encapsulation efficacy  
22 of insulin nanoparticles were 171.2 nm, 0.23 and 97.93%, respectively. Approximately 40% of  
23 encapsulated insulin was released from the nanoparticles within 2 h. To increase serum insulin  
24 concentration and produce an excellent hypoglycemic response, the nanoparticle formulation

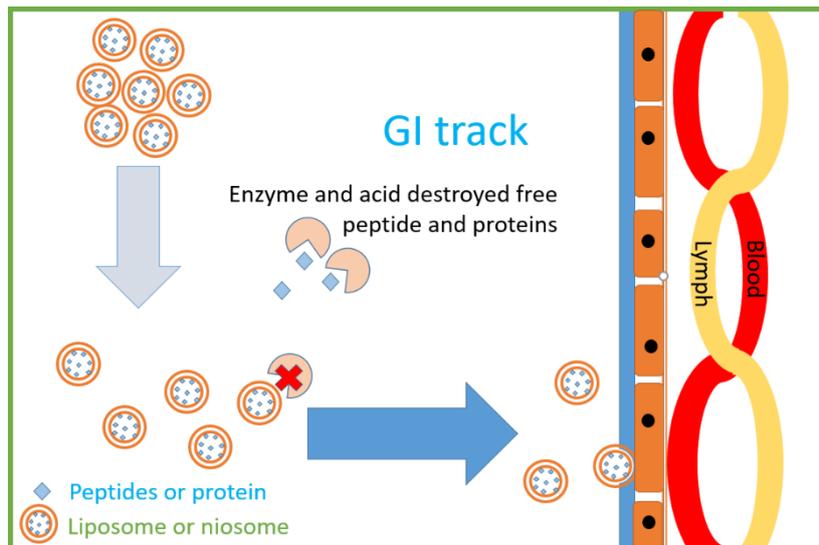
1 was quite effective (Xu et al. 2018b). Some recent studies about fabrication the oral delivery  
2 system for peptides and proteins are reported in Table.1

### 3 **6. Nanoemulsion carrier-based delivery system**

4 Nanoemulsions are drug delivery systems in which immiscible liquids are mixed to form a  
5 single-phase by adding suitable surfactants or mixing to produce a droplet, otherwise known  
6 as a micelle with a diameter range of approximately 0.1-100 nm (Sun et al. 2012). Due to  
7 unique structure and properties, their small droplet size carrier packages, the possibility of  
8 manufacturing with biocompatible materials, enhanced dissolution rate, solubility, diffusion  
9 through an unstirred aqueous layer and improved mucosal permeability, attention to such  
10 systems of nanoemulsions has increased recently (Gao et al. 2011; Gurpreet and Singh 2018;  
11 Rai et al. 2018; Singh et al. 2017). Nanoemulsions have a protective effect on the GI  
12 environment, improving the membrane fluidity, and transient opening of tight junctions caused  
13 by lipid constituents or surfactants components of these nanoemulsion formulations. It has also  
14 been commonly used to enhance the stability of drugs such as peptides and proteins (Jirwankar  
15 et al. 2020; Khaleel Basha et al. 2020; Li et al. 2013). Sun et al. (2012) designed a  
16 nanoemulsion delivery system for oral delivery of bovine serum albumin as a model protein  
17 drug. This formulation has demonstrated more than 90% encapsulation efficiency and  
18 substantially increased protein stability while preserving high levels of bioactivity of the drug  
19 (Sun et al. 2012). Li et al. (2013) developed modified nanoemulsions with alginate/chitosan for  
20 oral delivery of insulin. The in vitro analysis showed well-preserved nanoemulsion integrity in  
21 simulated gastric fluids and noted responses in both control and diabetic rats groups (Li et al.  
22 2013).

### 23 **7. Lipid bilayer vesicles carrier-based delivery system**

1 Liposomes and niosomes are one or more lipid bilayer vesicles. The lipid bilayers in liposome  
2 and niosome are formed by the self-assembly of phospholipids and non-ionic surfactants,  
3 respectively. Both hydrophilic and hydrophobic molecules are encapsulated in liposome and  
4 niosomes. Studies show that liposomes and niosomes can be prescribed by different routes of  
5 administration, such as the oral route (Ge et al. 2019; Nguyen et al. 2016; Niu et al. 2014;  
6 Shalaby and El-Refaie 2018; Tan et al. 2010). Entrapment of peptides and protein in lipid  
7 bilayer vesicles can protect them from enzymatic and acid degradation, increase absorption and  
8 bioavailability in the oral prescription that schematically shows in Figure 2. (Liu et al. 2020;  
9 Nguyen et al. 2016; Pardakhty et al. 2007; Tan et al. 2010). Varshosaz et al. (2003) used  
10 Sorbitan Monoester as a non-ionic surfactant to preparative niosomes for oral delivery, the  
11 result showed niosomal formulations of insulin are stable and protects insulin from trypsin and  
12  $\alpha$ -chymotrypsin (Varshosaz et al. 2003). Al-Remawi et al. (2017) prepared Chitosan/lecithin  
13 liposomes as oral delivery systems for insulin. The result showed oral liposomal formulations  
14 were more effective than the oral formulations of free insulin in rats (Al-Remawi et al. 2017).  
15 In liposome or niosome type, some modifications such as chitosan coating, PEGylated, Folate  
16 targeted, etc., increases their potential for oral delivery (Al-Remawi et al. 2017; Moghassemi  
17 et al. 2015; Shalaby and El-Refaie 2018; Yazdi et al. 2020).



1

- 2 Figure 2. Schematically shows lipid bilayer vesicles can protect from GI enzyme, acid
- 3 environment and increase absorption of peptides and proteins

Table 1. Some recent studies in preparation or use of the oral delivery systems for peptides and proteins

<b>Peptides and proteins</b>	<b>Carrier type</b>	<b>Main Material</b>	<b>Main observation</b>	<b>Reference</b>
Bovine serum albumin (model protein vaccine)	Modified Nanoparticles	Chitosan and Eudragit® L100	Significantly protect the protein against the enzymes and gastric environment	(Xu et al. 2018a)
Insulin	Nanoparticles	Chitosan	The blood glucose level through oral administration effectively controlled in diabetic rats	(He et al. 2017)
Glucagon like peptide-1 and Dipeptidyl	Nanoparticles	Poly(lactic-co-glycolic acid) and Polyvinyl alcohol	Blood glucose levels have reduced following oral administration of the nanoparticles	(Araújo et al. 2016)

peptidase-4 inhibitor				
Insulin	Modified Nanoparticles	Poly(lactic-co-glycolic acid), Cationic octa-arginine peptide and Specific anionic phosphoserine	Administration of insulin-loaded NPs have higher oral bioavailability in diabetic rats	(Wu et al. 2018)
Interferon alpha	Nanoparticles	Chitosan	Nanoparticles increase the oral bioavailability of interferon alpha that can be found in plasma	(Cánepa et al. 2017)
Cp1-11 peptide/insulin	Nanoparticles	Chitosan and Alginate	Nanoparticles can protect insulin against proteases in the gastrointestinal tract that led to degradation	(Chen et al. 2019)
Insulin	Nanoparticles	Silica	The permeation of nanoparticles enhanced both in vivo and in vitro study without toxic effect	(Lamson et al. 2020)

Ovalbumin	Nanoparticles	Cyclodextrin and Chitosan	Nanoparticles could enhance intestinal absorption	(He et al. 2019)
Insulin	Modified Nanoparticles	Deoxycholic acid and Chitosan	Degradation of insulin in the epithelium is significantly prevented	(Fan et al. 2018)
Recombinant Human Insulin	Modified Liposome	Egg phosphatidylcholine and Cholesterol	In diabetic mice reduction of blood sugar in 1 h and maintained up to 8 h	(Shalaby and El-Refaie 2018)
Insulin	Noisome	Olyoxyethylene alkyl ether surfactants or Sorbitan monostearate and Cholesterol	Decreased levels of blood glucose and elevated serum insulin in animal models	(Pardakhty et al. 2011)
Long tumor peptide and the	Liposome	1,2-distearoyl-sn-glycero-3-phosphocholin and Cholesterol	Positive therapeutic results were demonstrated in mouse model	(Naciute et al. 2020)

Toll-like receptor ligand Pam2Cys				
Cyclosporine A	Noisome	Tween 60, Span 60 and Cholesterol	The bioavailability of niosomal formulation of Cyclosporine A is increased with sustained release profile in albino rabbits	(Rehman et al. 2021)
Insulin	Noisome	Span 60 and Cholesterol	Niosomal formulation was able to facilitate insulin transport across intestinal membrane models	(Moghassemi et al. 2015)
Insulin	Modified Liposome	Hydrogenated soya phosphatidylcholine, Methoxy polyethylene glycol	Liposomes significantly increased insulin absorption through intestinal epithelia	(Yazdi et al. 2020)

		distearylphosphatidylethanolamine and Cholesterol		
Insulin	Liposome	Egg yolk lecithin, Cholesterol and 1,2-dioleoyl-3- trimethylammonium-propane	Remarkable ability to penetrate mucus and intestinal epithelial absorption.	(Wang et al. 2019)
Salmon calcitonin	Nanoemulsion	Sodium oleate and Sodium deoxycholate	Formulations significantly protected peptides from degradation by enzymes	(Jirwankar et al. 2020)
Insulin	Nanoemulsion	Alginate/Aloe vera	Insulin translocation in the cell monolayer is very promising.	(Khaleel Basha et al. 2020)
Teriparatide	Nanoemulsion	Oleic Acid, Labrasol and Plurol oleique	A sustained release profile was achieved following the oral administration and	(Altaani et al. 2020)

			improvement effects in osteoporosis animal model	
Insulin	Modified nanoemulsion	Phospholipid and Ethyl oleate	Higher oral bioavailability than that of oral insulin solution in diabetic rats observed	(Hu et al. 2019)
Coenzyme Q10	Nanoemulsion	Soybean oil, Lecithin and Octenyl succinic anhydride modified starch	Bioavailability increased 1.8-fold, compared with coenzyme Q10 dissolved in oil	(Niu et al. 2020)
MAGE1-HSP70/SEA (protein vaccine)	Modified Nanoemulsion	Soybean oil, Pluronic 188, Span 20, Tomato lectin	The levels of antibody induced by antigen in Nanoemulsion via the oral route was higher than other group	(Long et al. 2019)

## 1 **Conclusion**

2 Oral administration is one of the most widely used routes of prescribing drugs due to its greater  
3 compliance in most patients and fewer side effects. Peptides and proteins, due to their  
4 hydrophilic structure and large molecules, and their sensitivity to degradation by enzymes and  
5 acids, cannot be adequately absorbed and have high bioavailability when used without any  
6 carrier or delivery systems by the oral route. Injection routes are more commonly used for  
7 proteins administration. The use of new carrier-based drug delivery systems, however, can be  
8 a suitable alternative for oral peptides and protein delivery with increased stability, enhance  
9 uptake, and bioavailability. Studies on carrier-based drug delivery systems such as  
10 nanoparticles, nanoemulsions, and bilayer vesicle systems demonstrate the ability of these  
11 systems to improve the oral delivery of peptides and proteins such as insulin, teriparatide,  
12 interferon alpha, and coenzyme Q10. The use of these systems results in increased absorption,  
13 protected, and reduces the effect of degrading enzymes and acid on peptides and protein finally  
14 increases their bioavailability. Therefore, with the existing studies in this field, it seems that in  
15 the future, carrier-based drug delivery systems can be used for oral administration of peptides  
16 and proteins.

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## 20 **Compliance with Ethical Standards**

## 21 **Conflict of interest**

22 The authors declare that there are no conflict of interest.

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