IJPSR (2022), Volume 13, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 January 2022; received in revised form, 18 May 2022; accepted 06 June 2022; published 01 September 2022

CONCERNS AND LIMITATIONS OF MATERIALS FOR ORAL DELIVERY OF INSULIN

Harish Kumar Chaudhary [1], Vandana [1] and Amita Malik [* 2]

Department of Chemistry [1], Dyal Singh College, University of Delhi, New Delhi - 110003, Delhi, India.
IFTM University [2], Moradabad, Lodhipur Rajput - 244102, Uttar Pradesh, India.

Keywords:

Polymers, Biodegradable hydrogels, nanoparticles, Liposomes, Oral delivery, Insulin

Correspondence to Author:
Dr. Amita Malik

Professor,
IFTM University,
Moradabad, Lodhipur Rajput - 244102, Uttar Pradesh, India.

E-mail: amitamalik@dsc.du.ac.in

ABSTRACT: Insulin is commonly administered to diabetic patients sub-cutaneously and has shown poor patient compliance. The problem lies with the delivery of proteins and peptides to the body, for which oral, transdermal, vaginal, rectal, and pulmonary routes have been explored for proteins like insulin. Still, so far subcutaneous route has delivered the best results. This results in fear of the patients due to the prick caused by the subcutaneous delivery. To overcome these nuances, work has been carried out on delivering insulin orally. Different molecules have been extensively studied to deliver insulin orally. This review article covers the various materials exploited for the delivery of peptides like insulin, *viz*. polymers, nanoparticles, liposomes, and many more that have been evaluated as a vehicle for the oral delivery of insulin. Polymers that are naturally obtained like chitosan and its subsidiaries, alginates, γ-PGA based materials, starch-based nanoparticles, and manufactured polymers like PGLA, P(MAA-g-EG), PLA, PEA Poly(alkyl cyanoacrylate) Nanoparticles, Solid Lipid Nanoparticles, Targeted Nanoparticles and Gold Nanoparticles have been discussed for a better understanding of oral delivery.

INTRODUCTION: Diabetes mellitus, a disease associated with malfunctioning of the islet cells present in the pancreas to produce a sufficient amount of insulin or sometimes due to less sensitivity of host cells to endogenous insulin, differentiated as type I and type II diabetes of which type II causing less than 50% [1], has emerged as a major problem for healthy wellbeing over the years and caused considerably high mortality. Almost 30 years ago, therapeutic protein such as insulin was used for the first time. Later, the regulatory approval by USFDA in 1982 allowed insulin as a major therapy for diabetes [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(9).3357-74

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(9).3357-74

However, the problem lies with the delivery of proteins and peptides to the body though, for which oral, transdermal, vaginal, rectal, and pulmonary routes have been explored for proteins like insulin. Still, so far subcutaneous route has delivered the best results; nevertheless, at the same time is often feared by the patient due to the prick associated with the delivery. In this context, delivery of insulin by oral route has gained importance. The β-cells of the pancreas release the insulin directly to the hepatic portal vein and are carried to the liver, the main organ of concern.

Most commonly preferred routes of administering insulin, such as parenteral and nasal formulations directly deliver the drug to systemic circulation to bypass the first past metabolism causing a pronounced effect. However, the orally administered insulin first reaches the liver and peripheral tissue [3]. The oral route is simpler and economical and is the patient's first choice for its

comfort. Many problems are also associated with the effective availability of insulin to the body due to the enzymatic degradation, low absorption, and bioavailability. Thus, it is important to prevent its enzymatic degradation to ensure its availability. The human body is a delicate system equipped with several mechanisms to deal with any foreign agent introduced in the body by any route. A deeper insight into molecular biology and biochemistry is required for the application of proteins and peptides for therapeutic usage.

Several approaches such as permeation enhancers, enzyme inhibitors, enteric coatings and polymeric carriers like hydrogels have been used to account for oral administration. Hydrogels have gained importance due to their remarkable properties, such as the ability to retain a large amount of water, excellent biocompatibility and their mechanical properties, which suit the body. After their discovery in the 1960s by which trele and Lim, hydrogels were successfully used for contact lenses. Due to their novel properties and structure, these hydrogels can be tailored precisely for the desired therapeutic delivery of the drug.

Insulin Absorption and GI Tract: The GI tract is a series of hollow organs joined in a long, twisting tube from the mouth to the anus. The hollow organs are the mouth, esophagus, stomach, small intestine, large intestine and anus that make up the GI tract. The liver, pancreas, and gallbladder are the solid organs of the digestive system. These solid organs do not play any significant role in oral delivery. The proteins and peptides that are often used for oral delivery have to face the following challenges

a. Proteins and peptides are denatured in the acidic pH of the stomach or by digestive enzymes and are therefore inactivated. Theproteolytic enzymes present, such as pepsin in the stomach and trypsin, α-chymotrypsin and carboxypeptidase in the intestine, are major concerns. Further, it has been found that α-chymotrypsin alone degrades the protein as high as 10 times in comparison to trypsin [4].

b. The passage of drugs from the epithelial membrane to the bloodstream is quite difficult due to their poor permeability.

All the hollow organs such as the mouth, esophagus, stomach, small intestine, large intestine, and anus that make up the GI tract were investigated for oral delivery. It was found that in the small intestine, due to the presence of structures such as microvilli, specialized cell micro vessels have high absorption ability and are the best target site to deliver the drug in a short time orally. M cells in the small intestine are well known for their transport activity and low lysosomal activity. They can transport a foreign material such as a drug from the intestine lumen to lamina propria, as shown in **Fig. 1.**

The absorption power and potential of microvilli and microvessels are so large that drugs can be easily delivered to the bloodstream, systemic absorption, or the diseased cells, as in diabetes. Another part of the GI Tractis, the colon, which has been investigated for oral delivery, was thought to be advantageous as proteolysis activity of enzymes is very low in this part. However, due to the presence of bacteria, longtime systemic absorption and the presence of fecal matter have not been able to give good results and is therefore not considered much important.

Hydrogels are hydrophilic polymers with three-dimensional crosslinked networks. Peppas *et al.* 2000 [5], have classified the hydrogels based on the nature of the polymer, preparation method, crosslinking reaction, physical structure, and environmental stimuli.

They have high water or biological fluid retention capacity while remaining insoluble. Hydrogels, by their complexion properties, can remain stable in uneven conditions of the stomach and protect the drug from denaturation by acidic pH or digestive enzymes.

They can thus facilitate the drug release in the upper intestine with fewer enzymes, large surface area, and neutral pH, resulting in more than 90% absorption of nutrients.

Here they are de-complexed and, due to the ionic repulsion in such an environment, increase in the mesh size, thus swelling up the polymer at high pH **Fig. 1.**

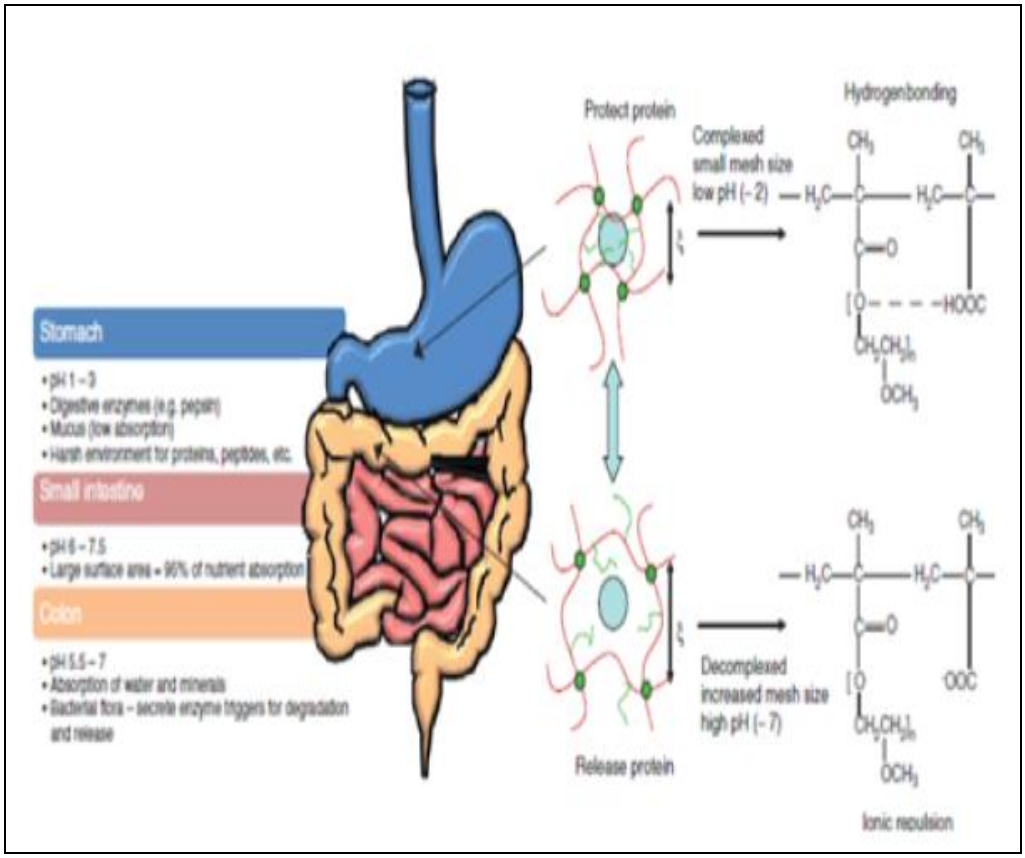

FIG. 1: PHYSIOLOGY OF GI TRACT, COMPLEXION AND DECOMPLEXION OF HYDROGELS

Polymers such as chitosan, dextran, alginate derivatives, and PGLA have been successful to a large extent in countering the enzymatic degradation and increasing the absorption of orally administered insulin. Charge on hydrogel also affected the swelling behavior; anionic hydrogel network can swell in solutions at pH > pKa due to repulsion of ions whereas cationic hydrogels swell at pH < pKa as the cationic pendant groups are protonated at pH less than pKa [6].

Nowadays, smart hydrogels sensitive to pH, temperature, light electric, and magnetic fields are called smart hydrogels. Drug delivery is a swelling-dependent phenomenon, particularly for hydrogels. An encapsulation study by Victor and Sharma 2002, for β-cyclodextrin insulin complex in PMAA based hydrogels showed that lower crosslinking increased the degree of swelling of hydrogels [7]. Temperature sensitivity, when related to pH can produce twofold benefits. Zhang *et al.* 2012 synthesized several pH-dependent thermo sensitive hydrogels using poly (N-isopropyl acrylamide) (PNIPAAm) and poly (methacrylic acid)(PMAA) with biodegradable crosslinker such as acryloyl-poly (ε-caprolactone)-2-hydro-ethyl methacrylate, such smart hydrogels in varying amounts of PNIPAAm released 60% of insulin in the intestine passing unmolested through Simulated Gastric Fluid (SGF) [8]. Oral insulin delivery shows lesser results due to fast degradation in the stomach with acidic pH. Insulin, a hydrophilic protein with a relative molecular mass of 5800 Da, difficult to be encapsulated, consists of 51 amino acids [9].

It is composed of two polypeptide chains in monomeric form, an A-chain of 21 amino acids and a B-chain of30 amino acids. A and B chains are joined together through two disulfide bonds. Another feature of insulin is its structural variation as it occurs as a monomer, dimer, tetramer, and hexamer. At a 0.1mM concentration occurs as a monomer, dimerizes in pH range 4-8, above 2mM occurs as hexamer at pH 7 [10]. The structural variation affects the rate of degradation; bile salts increase the rate of degradation by six times to its monomeric form [11]. The high molecular mass and hydrophilic nature of insulin further decrease its bioavailability and absorption through par cellular and transcellular routes [12], for which receptor-mediated transcytosis mechanism has also been investigated [13]. Insulin also acts as a growth

hormone, whose higher doses in the GI tract for long use can cause cytokinetic changes. Insulin doses ranging from 25 to 60 IU/Kg are highly effective in oral formulations. The devices used for oral delivery create hypoglycemic effects and should not at the same time produce growth-related issues.

In a study by Donovan *et al.* 1990, it was observed that the bioavailability of drugs decreases as the molecular mass increases above 700 Da [14]. Developing a successful clinically approved drug delivery system interplay factors such as size, drug loading efficiency, encapsulation efficiency, zeta potential, peptide bioactivity, and release kinetics [15].

It is quite certain that reducing particle size affected the drug loading efficiency, influencing the insulin absorption; smaller sized particles promoted rapid burst release, and stronger bio-adhesiveness induced high absorption through ileum [16]. The Tran swell model is the most common model used for intestinal studies in which human epithelial colorectal adenocarcinoma (caco-2 cells) are used, caco-2 cells represent the main cell type in the intestine. Caco-2 cell monolayer is monitored by trans-epithelial electrical resistance (TEER) using a chopstick electrode. TEER values range from 300Ω/cm^2 to 1000 Ω/cm^2. High TEER values represent a tighter monolayer that reduces large molecules' paracellular transport, while values lower than 300Ω/cm^2 indicate monolayer disturbance or celltoxicity [17].

To account for all, insulin is loaded with hydrophobic carriers such as distearyl- dimethyl-ammonium bromide or soybean phospholipid. In addition, different strategies, for example, intestinal coatings [18], protein inhibitors [19] and penetration enhancers [20-24], and cell penetrating poly peptides [25] have been utilized. Nowadays, natural and synthetic biodegradable hydrogels are preferred. When insulin is administered orally, it first comes across an acidic pH of 1.2-3.0 in the stomach and pH of 6.5-7.5 in the small intestine. These abrupt changes in pH make it difficult for insulin to maintain its efficacy. To maintain the stability of insulin, it is enteric coated with pH-sensitive materials such as hydroxyl propyl methylcellulose phthalate (HPMCP), poly (carboxylate), but such modifications decreased the insulin release to 15.87% in an acidic environment and at the same time increasing the rate of release from 15 to 58.06% in the intestine [18]. Another issue is to prevent the hydrolysis of insulin by pepsin and other proteases in GI Tract, for which enzyme inhibitors such as aprotinin have been used.

However, the use of enzyme inhibitors showed adverse effects such as pancreatic hypertrophy, impaired protein digestion, and hampered body functions. When the loaded insulin reaches the intestine, the intestinal mucus layer has to be crossed to reach the intestinal epithelium; this negatively charged layer is highly selective as it allows nutrients, water, and small molecules but not pathogens.

Usually, neutral molecules pass easily while positively charged molecules are electrostatic ally attracted and useful; therefore, chitosan, a positively charged polymer, has been widely studied.

Also, some weak negatively charged polymers like poly (acrylic acid), poly (methacrylic acid), carboxymethylcellulose, and sodium alginate have also been studied to form hydrogen bonds through carboxylic ends with oligosaccharide branches of mucus. Farah Beneyttou *et al* 2021 developed imine-linked-covalent organic framework (nCOF) nanoparticles for oral delivery. These insulin-loaded nCOF showed insulin protection in digestive fluids and can be a promising candidate for oral delivery [26].

In a recent study by Han X *et al.* 2020, zwitterionic micelles for oral delivery these micelles could deliver insulin orally without opening tight junctions and reported >40% bioavailability [27].

Possible Routes for Delivery: Generally, there are three courses for oral insulin assimilation as shown in **Fig. 2**. In the first place, the thickly bunched M cells were confined on Payer's patches [28].

Secondly, through the transcellular course, where lipophilic particles are ingested through the cell membrane of enterocytes, paracellular path ways such as through the tight junctions (TJs) between two enterocytes [29] and lastly by receptor-mediated transcytosis.

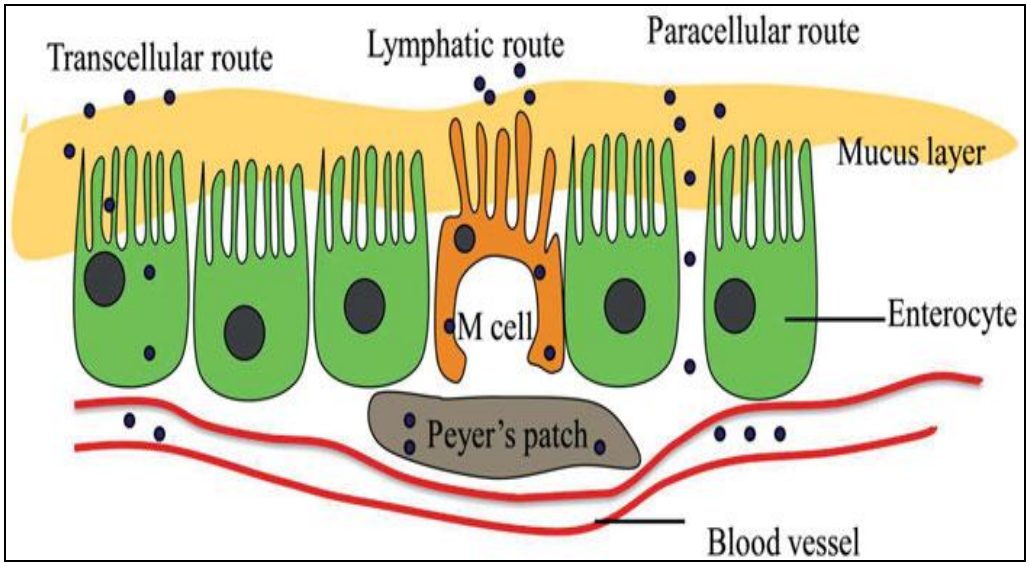

FIG. 2: THREE POSSIBLE ROUTES THROUGH THE INTESTINAL EPITHELIUM

Intestinal Lymphatic Route: The intestinal lymphatic route for delivery of the drug is widely used because it can bypass the first metabolism in the liver, thereby increasing oral bioavailability [30]. The transport of drugs and peptides to lymphatic vessels takes place on entering through Peyer's patches and then via M cells to lymphoid cells. Lipophilic drugs are known to be transported via the lymphatic system.

Transcellular Route: The transport of nanoparticles (NPs) through the transcellular pathway depends on the size of the nanoparticles and hydrophobicity. Transportation of particles lower than 300 nm takes place by means of enterocytes [31] while particles higher than 500 nm were effortlessly absorbed in jejuna Peyer patches [32]. Oral delivery of insulin loaded hyaluronic acid (ILHA) NPs through the transcellular route was investigated by Han *et al.*, 2012 and reported a reduction of 24% of plasma glucose levels in 2hrs in diabetic rats by ILHA NPs (insulin loaded hyaluronic acid nanoparticles) (50 IU/Kg) which were further reduced by 32-39% in 3-8 h whereas the group treated without HAloaded insulin showed no change in the blood glucose levels [33]. In another study, insulin-loaded dextran nanoparticles conjugation with Vitamin. B_{12}derivatives showed remarkable blood glucose reductions of 70% -75%, lasting for as large as 54 h, reflecting anti-diabetic effects in diabetic rats [34, 35].

Paracellular Route: Hydrophilic molecules can only pass through the paracellular route however, due to tight junctions, it becomes difficult for them to pass, which can be eased if permeation enhancers are used [36]. The opening of tight junctions depends more or less on the concentration of Ca^{2+} ions; the opening of tight junctions takes place due to the lowering of Ca^{2+} ion concentrations, while permeability across tight junctions increases by the addition of chelating agents such as ethylene glycol tetraacetic acid [36] and diethyl enetriaminepenta acetic acid [37].

Other polymers, including poly acrylic acid derivatives and chitosan, act by reversibly opening tight junctions and enhancing permeability [38-40]. Hydrogels based on poly (acrylic acid) and its derivatives have the capacity to bind Ca^{2+} and have shown promising results for oral delivery of insulin. The insulin-loaded poly (acrylic acid) hydrogels have shown 10 times higher relative bioavailability (6.59%) when administered orally in comparison to free insulin administered orally (less than 0.5%) [39-40]. However, opening tight junctions also allows bacterial toxins to be transported, which is a matter of big concern.

Receptor-Mediated Transcytosis: In a study by Ziv and Bendyan *et al.* 2000 receptor-mediated transcytosis was explored for insulin absorption [41]. For such transport, insulin was bonded to specific receptors on the apical plasma membrane, passed through deep invaginations of the lumen plasma membrane, and then to enterocytes releasing insulin into the interstitial spaces. The ligands such as transferrin, lectins, Vitamin B12 *etc.*, have been

used for receptor-mediated transcytosis by binding to respective receptors at the apical plasma membrane. Such a mechanism is used in several targeted NPs preparations [34-35].

Natural Polymers:

Chitosan: Chitosan (CS), a natural polysaccharide commonly obtained from crustacean shells and insects are derived from the deacetylation of chitin, a biopolymer present in these crustacean shells and insects. Glucosamine and N-acetyl-glucosamine are the main contents of chitosan. It is biocompatible, biodegradable, and protective in nature [42]. Chitosan is used for oral insulin delivery primarily due to its ability to open tight junctions reversibly and its mucoadhesive property [43-44]. The mechanism of drug release is shown in **Fig. 3.**

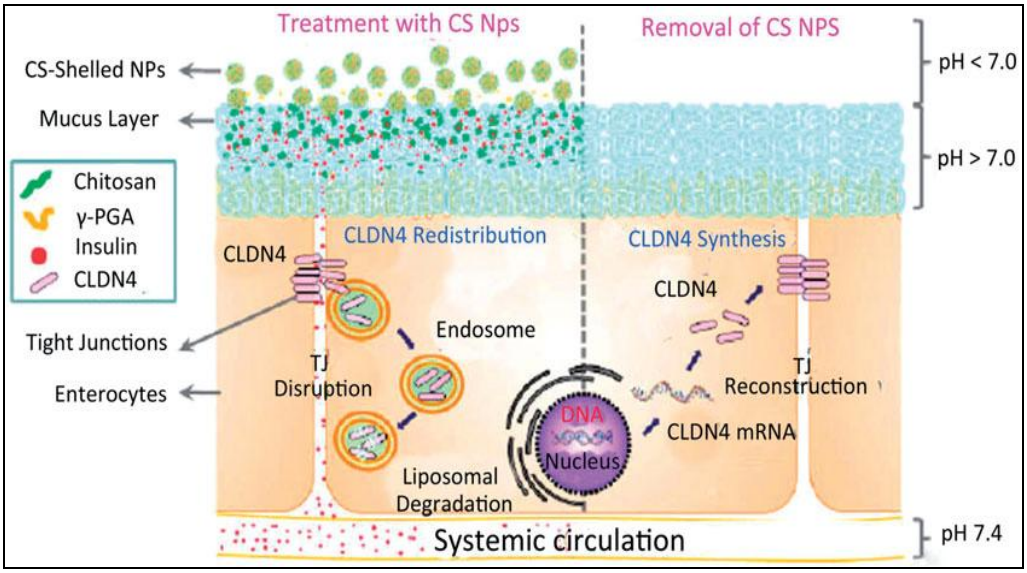

FIG. 3: SCHEMATIC ILLUSTRATION OF THE REVERSIBLE OPENING OF TIGHT JUNCTIONS BY CHITOSAN (SUNG *ET AL*, 2012) [45]

In a study, the iron oxide NPs obtained by laser ablation and encapsulated in chitosan showed a remarkable decrease in blood glucose levels to as low as 51% in diabetic rats when administered orally [46]. This may be taken as a breakthrough for site targeted drug delivery which can be developed due to the magnetic properties of NPs.

Chitosan Derivatives: Chitosan is mildly acidic (pKa = 6.5). Being insoluble in a neutral environment, it starts losing its charge, thereby causing loss of its ability to open tight junctions mucoadhesive properties [47]. Hence, its quaternized, thiolated, or carboxylated derivatives have been prepared to counter and have been evaluated for oral delivery [48]. Quaternized Chitosan (QC), due to its ability to retain a positive charge in a neutral environment, increased its residence time and bioavailability [49]. In a study, QC showed stronger electrostatic interaction with mucus to as large as 95% in comparison to chitosan which has shown 72% adhesion [50]. However, a high positive charge of QC causes toxicity to cell membranes. Chen *et al.* found that thiolated chitosan had more mucoadhesive properties than unmodified CS. Thiolatedtrimethylchitosan-cysteine (TMC-Cys) was prepared by forming disulfide bonds with cysteine to improve the mucoadhesion and the permeation capacities of thiolated polymers for administering oral insulin resulting in increased insulin absorption from 1.7 to 2.6 times through rat intestine [51].

Chitosan, when carboxylated, showed increased water solubility due to negatively chargedcarboxylate ions [52-53] and synthesized carboxylated chitosan nanoparticles by grafting poly(methyl methacrylate) which were investigated for oral delivery of insulin at 25 IU/kg and found 9.7% pharmacological bioavailability with long-lasting hypoglycaemic effect [54]. Lauryl sulfated chitosan (LSCS), an amphiphilic CS derivative, was studied for oral delivery of insulin and showed the non-toxic nature of LSCS with improved mucoadhesivity of chitosan protection against enzymatic degradation and the ability to open tight

junction's reversibly [55]. Rekha, *et al.* modified CS to incorporate both hydrophilic and hydrophobic characters, balancing of charge being quite important for insulin absorption in the GI tract [56].

They prepared lauryl succinyl chitosan using Sodium TPP as a crosslinker, and amino groups of chitosan were covalently bonded to 2-dodecyl succinic-1-yl anhydride (LSA). The hydrophobic character of lauryl sulfate and the hydrophilic nature of succinic anhydride improved the mucoadhesive and permeability in comparison to CS particles. Three different preparations with varying amounts of free amino groups were synthesized and loaded with insulin, prepared with 68% free amino group when administered in dose 60 IU/Kg reduced blood glucose level by 34% for a period of 6 hr. In contrast, native insulin loaded CS particles reduced BGL by 17% only.

In another study by Elaysed *et al.*, insulin-chitosan was complexed with oleic acid, Plurololeique (cosurfactant), and Labrasolsurfactant [57]. This composition showed a significant decrease in glucose levels in diabetic rats for 24 h when a 50IU/ Kg dose was administered orally. Ukai H, *et al.* used Labrasol-related formulations for oral delivery of these formulations Capyrol 90 was the most effective additive, which showed improved insulin absorption in the intestine *via* paracellular route [58]. Sharma D, *et al.* used oleic acid grafted chitosan zinc –insulin complexes for long term glycemic control [59].

In a recent study by Momoh, *et al.*, oil-in-water (o/w) emulsions were prepared using light liquid paraffin as the oily phase and various combinations of Tween® 80 and snail mucin powder. These microemulsions were insulin-loaded and studied for oral delivery, which showed a hypoglycemic effect for as long as 16 h [60].

Alginate Derivatives: Alginate, the apoly-anionicnatural polymer obtained from brown seaweed, is composed of α-L-guluronic (G) and β-D-mannuronic (M) acid residues linkedby(1→4)-O-glycosidicbonds. The pKa values of the M and G acid residues are 3.5 and 4.0, respectively. Thevarying ratios of β -D-mannuronopyranosyl and α -L-guluronopyranosyl units have always been used widely for preparing microparticles [61]. Alginate gels are formed by ionic crosslinking with cations, primarily Ca^{2+} ions, which further help in the drug retention within the gel matrix [62-63]. However, alginate beads often show low encapsulation efficiency and rapid drug release due to the large porosity of beads.

When chitosan and dextran sulfate is added to alginates, the low encapsulation efficiency ca n be improved [64-66]. To this chitosan - dextran sulfate, polyethylene glycol - albumin shell was supplemented, which lowered the proteolytic activity on insulin. Such insulin loaded nanoparticles lowered the glucose levels by as high as 70%, which lasted for 24 h [67]. In another study, multilayer nanoparticles of alginate and dextran sulfate coated on poloxamer and calcium stabilized by chitosan and albumin were prepared by Woitiski *et al.* [68].

These insulin-loaded nanoparticles reduced the blood glucose levels by 40% lasting for over 24hrs when administered orally to diabetic rats. In another study by Li *et al.*, chitosan, alginate, and $CaCl_2$ were dispersed in the oily phase comprising 68.5% Labrafac CC, 25% Span™ 80, and 6.5% phospholipid [69]. The emulsion so obtained was mixed into aq. solution of 3% Cremophor EL (a castor oil derivative). The nanoparticles obtained from the above composition were loaded with insulin when administered orally decreased blood glucose levels by 7.5-8.2%. Hebrard, *et al.* prepared hydrogel microparticles using whey protein and alginate [70].

Whey protein, a naturally obtained polymer with good nutritional value, can exist in different physical states such as foam, emulsion, and gel. The study revealed that such insulin-loaded alginate/ whey protein microparticles showed resistance to enzymatic degradation and have as high as 98% drug encapsulation efficiency [71].

β-cyclodextrin polymers were synthesized by Huang *et al.*, 2010 using epichlorohydrin and choline chloride to enhance the association efficiency of insulin [72]. These cationic polymers were encapsulated into CS-alginate microspheres. Further studies showed that these NPs with particle sizes ranging from 146 to 338 nm effectively protected insulin in the GI tract and have an

association efficiency of 87%, such inclusion of β-cyclodextrin with CS-alginate microspheres increased the positive charge leading to an increase in protection against enzymatic degradation and absorption increase enhancing cumulative insulin release by 40% in SIF (simulated intestinal fluid) in comparison to pure CS-alginate microspheres which showed 18% insulin release. Still, at the same time, 40% insulin was also released in SGF (simulated gastric fluid) [73].

Sevil, *et al.* synthesized alginate and gum tragacanth (ALG-GT) hydrogel with or without chitosan (CS) and conducted an insulin study in SGF and SIF[74]. In SGF, the ALG-GT gel showed no considerable insulin release protecting insulin from burst release, whereas, in SIF, it showed 70% cumulative release.

At pH6.8 (SIF), which is higher than the pKa of alginate (3.38-3.65) and GT(~3), both polysaccharides behaved as strongly negatively charged gel leading to steric and electrostatic repulsion causing insulin release in SIF. ALT-GT gel without CS with higher ratios of GT promoted higher insulin release.

Further, ALT-GT gel with CS owing to its advantage for paracellular transport, mucoadhesive properties, positive charge, and abundant amino groups, protected insulin from gastric degradation, moreover, increasing GT ratios led to less firm structure and weaker polymer-polymer interactions in gel network facilitated insulin release in the intestine through electrostatic interaction.

Zhou *et al.*, prepared glucose-responsive nanoparticles (GR-NPs) by self-assembly with NI-CYS-ALG (nitroimidazole- L-cysteine – alginate sodium) polymer, this amphiphilic polymer showed less swelling at low pH causing low insulin release. In the presence of GR-NPs insulin remained in SIF was 75.30±6.78% while in SGF remained 84.95± 0.79% at 180 min, indicating insulin stability and less enzymatic degradation showing promising results for oral delivery [75].

Poly-γ-glutamic Acid (γ-PGA): Poly-γ-glutamic acid (γ-PGA) is a biodegradable, water-soluble, and non-toxic polymer. Chitosan and poly-γ-glutamic acid (γ-PGA) have been used to synthesize nanoparticles for oral delivery of insulin. Due to the smaller size and higher loading efficiency in comparison to purely CS nanoparticles [76]. CS/ɣ PGA nanoparticles have shown resistance to gastric acid owing to their pH-sensitive behavior but at the same time released the drug in the small intestine at a faster rate [77-79].

Moreover, when CS/ɣ PGA was covalently conjugated with diethyl-enetriaminepentaacetic acid(DPTA) to form CS/ɣPGA-DPTA system residence time of orally administered insulin was prolonged and prevented enzymolysis [37].

A crosslinked network of CS/ɣ-PGA nanoparticles was prepared by adding tripolyphosphate (TPP) and $MgSO_4$ and was compared with CS/ɣ-PGA nanoparticles; these CS/ɣ-PGA-TPP-$MgSO_4$ nanoparticles showed a larger retention of insulin.

Further, such a modification had an advantage as at pH 2.5, and pH 7.0 release of insulin was reduced significantly, and at the same time at pH 7.4 fast release of insulin was observed. These all suggest thatmore insulin is released when passed into the mucus layer [80].

Starch-Based Nanoparticles: Starch is another naturally obtained biodegradable polymer. Its gel and film formation properties are well known which can be exploited for oral delivery. Zhang *et al.,* prepared a pH-responsive copolymer comprising starch nanoparticles as the backbone with poly(L-glutamic acid)(PGA) as graft chains [81].

The grafted copolymer showed excellently pH-responsive properties in a research study. The *in-vitro* release experiment reflected insulin release was much slower in gastric juice (pH 1.2) than in intestinal fluid (pH 6.8).

In another study, an amphiphilic polymeric derivative was prepared by using polyethylene glycol (PEG) and hydrophobic starch acetate. Due to their pH-sensitive nature, these nanoparticles were able to open tight junctions and showed improved mucoadhesivitity [82].

Details of the different processes studied to evaluate the availability of insulin are given in **Table 1.**

TABLE 1: PROCESSES TO IMPROVE THE BIOAVAILABILITY OF INSULIN

Processes	Systems	Advantages	Disadvantages	References
Insulin Modifications	Distearyldiammonium bromide, soybean phospholipid	Hydrophobicity of insulin is improved		85, 69
Permeation Enhancers	Chelators such as EGTA,DPTA	Ca^{2+} ion chelation helps in opening TJs	Threat due to absorption of bacterial toxins	37
Enteric coatings	HPMCP	Sensitivity to pH	Fast release in the intestine	52, 18
Enzyme inhibition	Trypsin, chymotrypsin inhibitors	Protection from GIT degradation due to proteases	Hamper body functions	19
Bioadhesion	Chitosan, PMAA	Adhesion to mucus layer increases retention	Limitation by the mucus layer	45

Synthetic Polymers: In previous sections, our discussion was on naturally obtained biodegradable polymers from different sources which were modified in one way or other to get the desired results, but from now on, we will focus on the polymers which are prepared synthetically, whose structure, physical and chemical properties can be well controlled and are biodegradable; hence their drug release properties could be tailored to our use.

PLGA (poly (lactic-*co*-glycolic acid): PLGA, PLG, or poly (lactic-*co*-glycolic acid) is a copolymer that is used in several approved therapeutic devices, owing to their biodegradability and biocompatibility. PLGA is synthesized through ring-opening copoly-merization of two different monomers, the cyclic dimers (1, 4-dioxane-2,5-diones) of glycolic acid and lactic acid. Insulin is entrapped in PLGA nanoparticles through hydrophobic interactions [83], which is otherwise quite complicated due to the hydrophilicity of insulin. Yang *et al.* prepared insulin-loaded PLGA nanoparticles when administered the particles orally to diabetic rats, which showed a rapid decrease in blood glucose levels in 24 h [84]. In a study, it is seen that the negative charge on the surface of PLGA nanoparticles leads to weaker bioadhesive abilities compared with positively charged nanoparticles and was therefore subjected to cationic modifications by chitosan coatings, which resulted in improved bioavailability. These modified CS-coated PLGA nanoparticles had an advantage over PLGA nanoparticles as they reduced initial burst, strong mucoadhesion, prolonged resistance time, and increased insulin bioavailability [8]. In another study, Cui *et al* modified insulin in which dichloromethane, ethyl acetate 2% polymer (w/v) was added to insulin phospholipid complex, which was then added to 2% aqueous solution of polyvinyl alcohol. To improve the hydrophobicity soybean phospholipid was taken; such preparation reduced 57.4% blood glucose levels in 8 h, which lasted for12 hrswhen administered orally [85].

Hosseininasab *et al.,* synthesized triblock copolymer of PLGA-PEG by ring-opening polymerization of L-lactide and glycolide in the presence of PEG [86]. Two different molecular weights of PEG viz. PEG2000 and PEG 4000 were used, the size of such insulin-loaded PGLA-PEG NPs varied from 25-75 nm. The encapsulation efficiency of unmodified PGLA-PEG NPs, PGLA-PEG2000, and PGLA-PEG4000 was 69.5%, 73% and 78%, respectively, showing an increase in EE with the increase in molecular weight of PEG. The PGLA-PEG copolymers released the insulin in the intestine compared to PLGA-PEG hydrogels, which released insulin in the stomach. Hence, copolymer was able to protect insulin from enzymatic degradation in the GI tract.

Sheng *et al.,* synthesized N-trimethyl chitosan chloride (TMC) coated polylactide-co-glycoside nanoparticles (TMC-PLGA NPs) and loaded them with insulin to carry out the study for oral delivery [87]. These insulin loaded Ins TMC-PGLA NPs were prepared by double emulsion solvent evaporation method with size (247.6 ± 7.2 nm), zeta potential (45.2 ± 4.6 mV), insulin loading capacity (7.8 ± 0.5 %) and encapsulation efficiency (47.0 ± 2.9%). Ins TMC-PGLA NPs were able to partially protect the insulin from enzymatic degradation, mucus penetration in mucus-secreting HT 29-MX cells

was improved compared to unmodified PLGA NPs, and permeation across caco-2 cells took place owing to the opening of TJs. Ins TMC-PLGA NPs showed a stronger hypoglycemic effect in diabetic rats, indicating improved mucoadhesive properties leading to 2-fold higher bioavailability in comparison to unmodified PLGA NPs.

Wu *et al.,* synthesized PLGA/HP55 nanoparticles to investigate the oral delivery of insulin. PLGA/HP55 NPs were prepared using a modified multiple emulsion solvent evaporation methods (MSME) [88]. Nanoparticles prepared by multiple emulsions were larger in size in comparison to when prepared by the single emulsion method [89]. The encapsulation efficiency was up to 94%. When administered orally to diabetic rats with dose 50 IU/Kg showed a fast decrease in blood glucose level between 1h and 8h indicating better absorption in the upper intestine.

PLA: Poly (lactic acid) (PLA) has been used by Xiong *et al.,* in which Pluronic/PLA copolymer was prepared. Pluronic block copolymers, a synthetic polymers have been approved by USFDA as a food additive and pharmaceutical ingredient [90]. Due to their amphiphilic properties [91, 92] and permeation, the presence of PEO blocks in these polymers has shown a strong affinity to the small intestine. PLA-F127-PLA have been investigated for oral delivery, and these insulin-loaded vesicular NPs have been studied for hypoglycemic effect on diabetic rats.PLA units were attached to both ends of the Pluronic copolymer.

The PLA-F127-PLA vesicles loaded with insulin, when administered orally to diabetic mice with doses 50 IU/Kg reduced blood glucose levels within 4.5 h lasting for 23hrs by 70%. The release of insulin is affected by the size, molecular weight, block composition, and degradation rate [93] (Arogoa *et al.,* 2000). The study on PLA-F127-29 by has found that when loaded with insulin, these block polymers showed the presence of insulin inside the vesicular core and on the surface and, hence, can produce a sustained hypoglycemic effect [94]. These polymeric vesicles have an advantage over liposomes and coated liposomes owing to their smaller size and bilayer thickness which can be varied by varying molecular weight[95]Synthesized PLA and PLGA microparticles by w/o/w multiple emulsion solvent evaporation techniques were loaded with 5% bovine insulin showed 75% and 80% encapsulation efficiency respectively at pH 7.4. The size of particles varied from 40-53µm having a spherical shape with porous surfaces. Insulin being located on the surface showed an initial burst.

P(MAA-g-EG): Polyethylene glycol, when grafted on poly (methacrylic acid)(PMAA), is designated as P(MAA-g-EG). These complex anionic pH-sensitive hydrogels protected the drug from an acidic stomach environment and hence released the drug in the small intestine. In an acidic environment of the stomach due to hydrogen bonding between protons of carboxylic acid and the oxygen of PEG, the P(MAA-g-EG) network collapse as a result of complexation, thus protecting the insulin from the harsh environment of the stomach.

Further, as the pH increases above 4.8, deprotonating results in ionization and electrostatic repulsion, thus breaking of a complex polymer leading to swelling of polymer favoring the drug delivery as illustrated in Figure 2.P(MAA-g-EG) based hydrogels showed high encapsulation efficiency(> 90 %) and high absorption across the intestinal mucosa. Peppas and Klier first reported the pH-responsive nature of P (MAA-g-EG) and investigated the polymer for oral drug delivery [96].

They observed no hydrogen bonding between PEG tethers and carboxylic acid groups of the PMAA backbone, thus promoting mucoadhesion, which increased residence time and bioavailability. Mucoadhesive and site-specific effects of P(MAA-g-EG) hydrogels were further enhanced due to carboxylic acid pendant groups inacidic pH bound to Ca2+ ions. They resisted the enzymatic degradation by trypsin, a Ca^{2+} dependent enzyme. Kavimandan *et al. synthesized insulin-transferrin complex, consisting* of two insulin molecules and one transferrin molecule [97], transferrin, a ligand used for transport of iron and peptides absorption [98-99]. The complex conjugate showed resistance to proteolytic degradation. The complex was joined to P (MAA-g-EG) based hydrogels and investigated using the caco-2 cell model, and the receptor-mediated endocytotic pathway showed 22 times increase in insulin permeability as well as the

loosening of TJs, leading to increased paracellular transport. The study further showed an increase in transport by 14 times using insulin-transferrin complex in comparison to P(MAA-g-EG) loaded insulin. In another study on oral insulin delivery MAA based hydrogels were prepared by Kim and Peppas using photopolymerization [100]; these pH-responsive hydrogels were investigated for insulin release at pH 2.2 and pH 6.4, found best results for P(MAA-co-MEG) having MEG: MAA in the ratio of 1:4 and P(MAA-g-EG) with PEG 200, showed 5 to 7% bioavailability [16]. These hydrogels decreased the Ca^{2+} ion concentration, reducing enzymatic degradation and opening TJs, leading to an increase in permeability [101].

Wood *et al.,* 2008 tried to exploit the presence of N-acetyl-d-glucosamine sialic acid, the group found on intestinal M cells and normal absorptive cells of the intestine that can bind to wheat germ agglutin (WGA), a glycoprotein extracted from Triticumvulgare, thus increasing the residence time as well as absorption of insulin [102]. Mucoadhesive properties of P(MAA-g-EG) base hydrogels were improved with WGA by 17%. WGA binds to caco-2 cellsenterocytes as well as promoted receptor-mediated endocytosis [103]

Carr *et al.,* synthesized polymers based on Poly (methacrylic acid-co-N-vinyl pyrollidone) P(MAA-co-NVP) using methacrylic acid and N-vinyl pyrrolidone as monomer, and EGDMA was used for the crosslinking agent for oral delivery [104]. It was found that no insulin was released in acidic pH indicating more absorption in GI tract showed low transport across caco-2 cells. Sajesh and Sharma, 2011 tried to improvise P(MAA-co-NVP) by incorporating chitosan by ionic gelation technique. However, the system failed to show effective paracellular absorption [105].

Li *et al.,* 2020 synthesized pH-sensitive sodium carboxymethylcellulose and polymethyl acrylic acid (CMC/PMAA) semi IPN hydrogel using N's free-radical polymerization method, N- methylene-bis-acrylamide (NNMBA) [106]. The average diameter of CMC/PMAA hydrogel pores was found to be 62.45±13.10 mm compared to PMAA hydrogel, which has a pore diameter of 110.82±24.03. Theoretically, pore size should increase on an increasing amount of CMC [107]. However, CMC/PMAA hydrogel showed a decrease in pore size which may be due to increased entanglement of CMC with PMAA. The equilibrium swelling and swelling ratio (SR) were found to be 70.02±4.37 and 60.54±0.99 g/g respectively; drug loading capacity was determined to be 26.4±0.01%. The insulin loaded CMC/PMAA hydrogel was taken to release kinetics which showed cumulative release at pH 1.2as 26.66±2.67% and 46.14±3.62% at 2h and 14h, respectively, whereas at pH 6.8 the cumulative release was 57.47±4.88% and 85.86±6.00% at 2h and 6h. The insulin-loaded CMC/PMAA hydrogel (75 IU/Kg) showed a sustained decrease in blood glucose level starting from 4h and continuing to12h. However, less reduction in blood glucose level was observed at dose 50 IU/Kg.

PCL: Poly (ε-caprolactone)is a biodegradable polyester with a low melting point prepared byring-opening polymerization of ε-caprolactone using a catalyst such as stannous octoate & others. Polymeric nanoparticles were prepared using biodegradable poly (ε-caprolactone) and non-biodegradable poly cationic acrylic polymer (Eudragit RS) and were used for regular insulin delivery as well as part-loaded insulin delivery. It was observed that part-loaded PCL/ Eudragit-RS nanoparticles on oral administration to diabetic rats with a dose 50 IU/Kg led to a reduction of plasma glucose levels by 52%, lasting for 8h after administration [108]. Moreover, when compared to orally administering regular insulin-loaded PCL/ Eudragit-RS which showed 6-8 h hypoglycemic effect, part-loaded PCL nanoparticles showed a hypoglycaemic effect for 12-24 h [109]. This may be attributed to intestinal mucosa absorbed monomeric as part-insulin more rapidly than regular human insulin [108].

PEA: Poly (ester amide) sare biodegradable synthetic polymers. L-Lysine/L-Leucine based poly (ester amide) containing pendent -COOH groups were synthesized by He *et al.,* by solution polycondensation of three monomers and investigated for oral delivery of insulin. PEA microspheres were used to encapsulate insulin, leucine components on adjustment showed improved absorption of insulin. These PEA microspheres were insulin loaded and administered orally to streptozotocin-induced diabetic rats with a

dose of 60 IU/Kg showed reduction of plasma glucose levels by 49.4% within 5 h of administration and lasted for 8 h [31]. In another study, Arginine-based PEA (Arg-PEA) microspheres were used which further improved the reduction in plasma glucose levels [110].

Poly (alkylcyanoacrylate) Nanoparticles: Poly (isobutylcyanoacrylate), PIBCA, a tissue glue has been investigated for oral delivery of insulin due to its stability and biodegradability. Damage *et al.*, prepared insulin nanoparticles by polymerizing PIBCA [111]. These NPs showed a sustained reduction of blood glucose level after 2 h. The effect of encapsulated polymeric PIBCA NPs showed more site-dependent hypoglycemia in GIT, ileum showing the max absorption. PIBCA, a polymeric colloidal particle with less than 300 nm diameter, has an oily core (Miglyol 812) with poloxamer 188 as a surfactant. These insulin loaded NPs were studied for oral administration to diabetic rats, which showed a reduction of blood glucose level from 2 h after administration lasting for as long as 13 days. The study also indicated that the effect was more pronounced due to oil and surfactant agents protecting the insulin from proteolytic enzymes, while suspension in water did not show any effect [111].

Insulin-poly-butylcyanoacrylate nanoparticle (IPN) dispersed in soybean oil containing Tween-20 0.5% (v/v) and vitamin E 5% (v/v) (size 67 nm) and poly butylcyanoacrylate containing 0.5% (v/v) Tween20 (size 78 nm), these two formulations were prepared by Houet al which showed reduced blood glucose level when administered orally (50 IU/kg) to diabetic rats [112]. In poly (alkyl cyanoacrylate) nanoparticles composed of isopropyl myristate, caprylocaproyl macrogol glycerides, poly-glyceryl oleate, and insulin of size 200-400nm were dispersed and prepared by Graf *et al.;* this formulation showed reduced blood glucose levels for as long as 36 h when administered orally (100 IU/kg) [113]. Details of the different hydrogels studied are given in **Table 2.**

TABLE 2: TYPES OF HYDROGEL SYSTEMS AND THEIR DELIVERY SITES

	Formulation	Type	Site	Ref
A. Intestinal Delivery Systems				
Anionic	P(MAA-g-EG)	Synthetic	Small Intestine	96
	Alginate derivatives	Natural	Small Intestine and Colon	62, 63, 65, 66
	Hyaluronic acid Based	Natural	Small Intestine	27
Cationic	Chitosan derivatives	Natural	Small Intestine	48, 54, 55, 51
Amphiphilic	P(MAA-g-EG)	Synthetic	Colon	96
B. Intracellular Delivery Systems				
Cationic	Chitosan derivatives	Natural	Cytosol	48, 54, 55, 51
	CS-coated PLGA	Synthetic	Cytosol	8
	PEA	Synthetic	Small Intestine	31

Solid Lipid Nanoparticles (SLN): Nanoparticles of solid lipids of the colloidal range were first investigated in 1990 and were used in several formulations since then successfully. The biggest advantage of such SLNs as drug carriers lies in their reduced toxicity owing to lipid components, which further showed protection from proteolytic enzymatic degradation in GIT [114]. In another preparation, lectin-modified SLNs were prepared by Zhang *et al.* These NPs were further modified with wheat germ agglutinin-N-glutaryl-phospha-tidylethanolamine (WGA) and encapsulated with insulin; the advantage of such modifications being the protection of insulin from enzymatic degradation in GIT. These formulations showed a hypoglycaemic effect in rats when administered orally. The pharmacological bioavailability following oral administration of insulin-SLNs and WGA modified insulin-SLNs was 4.46% and 6.08%, respectively [115]. Witepsol 85E solid lipid nanoparticles (SLNs) coated with chitosan were prepared by Fonteet *et al.* for encapsulation of insulin [116]. The diameters of SLNs and chitosan-SLNs were 243 ± 10 nm and 470 ± 32 nm, respectively. When these CS coated insulin SLNs were administered orally to diabetic rats showed

reduced blood glucose levels for 24 h. In another study, solid nanoparticles containing octadecyl alcohol, cetylpalmitate, stearic acid, glycerylmonostearate, glycerylpalmitostearate, glyceryltripalmitate, and glycerylbehenate were prepared by Yang *et al.* These SLNs showed reduced blood glucose levels when administered orally (50 IU/kg) up to 24 h [117]. In a recent study, solid lipid nanoparticles with endosomal escape peptides were prepared byXu *et al.* These SLNs were loaded with insulin and administered orally (50 IU/kg), which showed a hypoglycemic effect in the first 3 h by 35% but reduced to 20% after 12 h [118].

Targeted Insulin Nanoparticles: A nanoparticle complex of insulin preloaded dodecylamine-graft-ɣ-polyglutamic acid micelles were crosslinked with N-trimethyl chitosan chloride (TMC) modified with a CSKSSDYQC peptide (goblet cell targeting peptide) by Jin Y *et al.*, such a modification improved the affinity towards epithelium. These novel complex insulin-loaded NPs showed long-lasting reduced BGL in diabetic rats when administered orally [119]. In another study by Pridgen *et al.*, PLA-PEG was synthesized using ring-opening polymerization with a free terminal maleimide group (PLA-PEG-MAL) to conjugate the Fc portion of IgG and nanoparticles were prepared. These NPs were targeted to neonatal Fc receptor (FcRn) can regulate the transport of IgG antibodies through the epithelium [120]. When administered orally (1.1 IU/kg) to wild-type mice, these insulin loaded NPs showed a prolonged hypoglycemic effect with a mean absorption efficiency of 13.4 % per hr compared to non-targeted NPs (1.2% per hr).

Insulin-loaded Gold Nanoparticles: Insulin-loaded gold nanoparticles have been prepared using a reducing agent such as sodium borohydride by Joshi HM *et al.* and administered orally to diabetic rats showing a reduction in blood glucose levels by 18% after 3 h of delivery [121]. In another preparation by Joshi H M *et al.*, chitosan was used as a reducing agent to prepare insulin-loaded nanoparticles and was administered orally (50IU/Kg) to diabetic rats. These NPs showed a hypoglycemic effect after 2 h by 30% after administration. The advantage of using chitosan was that it promoted penetration of the mucosal layer by NPs [122]. Nanoparticles used for oral delivery of insulin are illustrated in **Table 3.**

TABLE 3: TYPES OF NANOPARTICLES USED IN ORAL DELIVERY OF INSULIN

Polymer	Size(nm)	Animal	Dose	References
1. Chitosan	250-400	Diabetic rats	21 IU/Kg	[63]
Chitosan Derivatives				
A. Quaternized Chitosan	~265.4	-------	---------	[49]
B. Thiolated trimethyl chitosan +trimethyl chitosan-cysteine (TMC-Cys)	100-200	Diabetic rats	50 IU/Kg	[51]
C. Carboxylated chitosan + methyl methacrylate	251 to 319	Diabetic rats	15-100 IU/Kg	[52], [54], [53]
D. Lauryl sulfated chitosan	----	Diabetic rats	45 IU/ 100 mg	[55]
E. Chitosan + Oleic acid + Plurol oleique + Labrasol	108	Diabetic rats	50 IU/Kg	[57]
F. Alginate + Chitosan	748	Diabetic rats	25-100 IU/Kg	[62]
G. Chitosan + Dextran sulfate	527	Diabetic rats	50-100 IU/Kg	[64], [65], [66]
H. Chitosan + TPP (pentasodium tripolyphosphate) + Poloxamer 188	250 – 400	Diabetic rats	7-21 IU/Kg	[68]
I. Chitosan + γ-PGA	~200	Diabetic rats	30 IU/Kg	[76]
J. Chitosan + Alginate + Calcium chloride + Labrafac CC + Phospholipid+ Span 80 + Cremorphor EL	488	Diabetic rats	25-50 IU/Kg	[69]
2. PEGylated starch acetate	32	Diabetic rats	1.3 ± 0.1 IU/mg	[82]
SYNTHETIC POLYMERS				
1. PGLA Poly(lactic-co-glycolic acid)	>200	Diabetic rats	30mg/Kg	[84]
A. Chitosan-PGLA	135	Diabetic Rats	15 IU/Kg	[8]
B. PLGA + Phospholipid + PVA	104-428	Diabetic rats	20 IU/Kg	[85]
2. Polylactic acid (PLA-F127-PLA)	56	Diabetic mice	50 IU/Kg	[90]
3. P(MAA-g-EG) P(MAA-g-PEG)	200 nm at	Diabetic rats	50 IU/Kg	[96]

	pH 2.0 2µm at pH 6.0			
4. Poly(ε-caprolactone) PCL				
A. PCL and Eudragit® RS	331	Diabetic rats	25-100 IU/Kg	[109]
B. Aspart-PCL and Eudragit® RS	700	Diabetic rats	50 IU/Kg	[108]
5. PEA Poly (ester amide)				
L-Lysine/L-Leucine-based poly (ester amide)	---	STZ induced Diabetic rats	60 IU/Kg	[31]
6. Dextran				
A. Dextran + Vit. B 12	150-300	STZ induced Diabetic rats	20 IU/Kg	[34]
B. Dextran + Alginate + Chitosan + PEG + BSA	>1842 (90 %) >812 (50 %)	Diabetic rats	25 – 100 IU/Kg	[67]
C. Dextran + Alginate + Poloxamer + Chitosan + BS	396	Diabetic rats	50 IU/Kg	[68]
7. Polyalkylcyanoacrylate				
Poly(isobutylcyanoacrylate) PIBC				
A. PIBCA	300	Diabetic rats	100 IU/Kg	[111]
B. PIBCA + Poloxamer188(Surfactant) + Miglyol	145	Diabetic rats	100 IU/Kg	[111]
C. PIBCA + Tween 20	78	Diabetic rats	50 IU/KG	[112]
D. PIBCA + Tween 20 + Soyabean oil + vitamin E	67	Diabetic rats	50 IU/Kg	[112]
E. PIBCA +Isopropyl myristate + caprylocaproyl macrogol glycerides + polyglyceryl oleate	200 – 400	Diabetic rats	100 IU/Kg	[113]
8. Solid Lipid Nanoparticles (SLNs)				
A. Lecithin + stearic acid + poloxamer + wheat germ agglutinin-N-glutamyl-phosphatidylethanolamine	75.3	Diabetic rats	50 IU/Kg	[115]
B. Witepsol 85E	233 – 253	Diabetic rats	25 IU/Kg	[116]
C. Witepsol 85E + Chitosan	470 ± 32	Diabetic rats	25 IU/Kg	[116]
D. Cetyl palmitate-based solid lipid nanoparticle (SLN)	350	Diabetic rats	50 IU/Kg	[117]
E. Solid lipid nanoparticles with endosomal escape peptide	150 – 160	Diabetic rats	50 IU/Kg	[120]
9. Targeted insulin Nanoparticles				
A. N-trimethyl chitosan chloride + CSKSSDYQC peptide	342	Diabetic rats	50 IU/Kg	[119]
B. PLA-PEG + human polyclonal IgG Fc	63	Wild type mice	1.1 IU/Kg	[120]
10. Gold nanoparticles	35	Diabetic rats	50 IU/Kg	[122]
A. Chitosan – reduced gold nanoparticles	10 – 50	Diabetic rats	50 IU/Kg	[122]

CONCLUSION: Diabetes mellitus has become one of the common concerns in recent years, and to tackle such an issue, oral delivery of insulin has become the need of the hour. Although many studies have been carried out to improve the drug's loading efficiency and stability, desired results have not been met. Biodegradable hydrogels have been studied as excellent carriers for drug, protein, and peptide delivery due to their ability to get modified by hydrophilic/hydrophobic balance, which allows them to control and defer or speed up the drug transport. Hydrogels are especially significant as transporters for oral conveyance because they can be delivered anionic, cationic, or amphiphilic by fitting copolymerization measures with ionic parts to suit the uneven conditions of the GI Tract. Albeit this joining of ionic moieties prompts naturally delicate designs, and accordingly, there are various unanswered inquiries concerning the utilization of hydrogels as oral delivery vehicles that have to be answered.

ACKNOWLEDGEMENT: The authors are thankful to the college for providing us all support and infrastructure for carrying out an online literature survey for completing this article

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Sharma SK, Kant R, Kalra S and Bishnoi R: Prevalence of Primary Non adherence with Insulin and Barriers to Insulin Initiation in Patients with Type 2 Diabetes Mellitus - an Exploratory Study in a Tertiary Care Teaching Public Hospital, Eur. Endocrinol 2020; 16 (2): 143–147.
2. Leader B, Baca QJ and Golan DE: Protein therapeutics: a summary andpharmacological classification. Nat Rev Drug Dis 2008; 7 (1): 21-39.
3. Rekha MR and Sharma CP: Oral delivery of therapeutic protein/peptide for diabetes –future perspectives. Int J Pharm 2013; 440: 48–62.

4. Schilling RJ and Mitra AK: Degradation of Insulin by trypsin and o-chymotrypsin. Pharm Res 1991; 8: 721-727.
5. Peppas NA, Bures P, Leobandung W and Ichikawa H: Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm 2000; 50: 27–46.
6. Koetting MC: Peters JT, Steichen SD and Peppas NA: Stimulus Responsive Hydrogels: Theory, Modem Advances and Applications. Mater Sch Ere R Reports 2015; 93: 1-49.
7. Victor SP and Sharma CP: Stimuli sensitive polymethacrylic acid microparticles (PMAA)-Oral insulin delivery. J Biomater Appl 2002; 17: 125–134.
8. Zhang X, Sun M and Zheng A: Preparation and characterization of insulin-loaded bioadhesive PLGA nanoparticles for oral administration. Eur J Pharm Biopharm 2008; 45: 632-8.
9. Matsuura J. Powers ME, Manning MC and Shefter E: Structure and stability of insulin dissolved in 1-octanol. J Am Chem Soc 1993; 115: 1261-1264.
10. Hansen JF: The self-association of zinc-free human insulin and insulin analog B13-glutamine. Biophys Chem 1991; 39: 107-110.
11. Li Y, Shao Z and Mitra AK: Dissociation of insulin oligomers by bile salt micelles and its effect on a-chymotrypsin-mediated proteolytic degradation. Pharm Res 1992; 9: 864-869.
12. Drucker DJ: Advances in Oral Peptide Therapeutics. Nat Rev Drug Discov 2020; 19(4): 277–289. doi:10.1038/s41573-019-0053-0.
13. Fan JY, Carpentier JL, Gorden P, Obberghen EV, Blackett NM, Grunfeld C and Orci L: Receptor-mediated endocytosis of insulin: role of microvilli, coated pits and coated vesicles. Proc Natl Acad Sci USA 1982; 79: 7788-7791.
14. Donovan MD, Flynn GL and Amidon GL: Absorption of polyethylene glycols 600 through 2000: the molecular weight dependence of gastrointestinal and nasal absorption. Pharm Res 1990; 8: 863-868.
15. Ye, Mi. Kim, S and Park K: Issues in long-term protein delivery using biodegradable microparticles. J Control Release 2010; 146: 241-260
16. Morishita M, Goto T, Peppas NA, Joseph JL, Torjman MC, Munsick C, Nakamura K, Yamagata T, Takayama K and Lowman AM: Mucosal insulin delivery systems based on complexation polymer hydrogels: effect of particle size on insulin enteral absorption. J Control Release 2004; 97: 115-124.
17. Okada T. Narai A and Matsunaga S: Assessment of the marine toxins by monitoring the integrity of human intestinal Caco-2 cell monolayers. Toxicol *In-vitro* 2000; 14(3): 219-26.
18. Zhao X, Shan C and Zu Y: Preparation, characterization, and evaluation in vivo of Ins-SiO (2) -HP55 (insulin-loaded silica coating HP55) for oral delivery of insulin. Int J Pharm 2013; 454: 278–84.
19. Werle M, Loretz B and Entstrasser D: Design and evaluation of a chitosan-aprotinin conjugate for the peroral delivery of therapeutic peptides and proteins susceptible to enzymatic degradation. J Drug Target 2007; 15: 327-33.
20. Degim Z,Unal N and Essiz D: The effect of various liposome formulation insulin penetration across Caco-2 cell monolayer. Life Sci 2004; 75: 2819-27.
21. Lamson, N. G, Fein, KC, Gleeson JP, Xian S, Newby A and Chaudhary N: From Farm to Pharmacy: Strawberry-Enabled Oral Delivery of Protein Drugs. BioRxiv preprint. (2020a). doi:10.1101/2020.03.11.987461.
22. Lamson NG, Berger A, Fein KC and Whitehead KA: Anionic Nanoparticles Enable the Oral Delivery of Proteins by Enhancing Intestinal Permeability. Nat Biomed Eng 2020; 4 (1): 84–96. doi:10.1038/s41551-019-0465-5.
23. Zhang X, Ma GH and Su ZG: Novel poly (L-lysine) particles for gene delivery. J Control Release 2011; 152: 184-6.
24. Zhang Y, Wei W and Lv P: Preparation. and evaluation of alginate-chitosan microspheres for oral delivery of insulin. Eur J Pharm Biopharm 2011; 77: 11-19.
25. Guo F, Ouyang T and Peng T: Enhanced oral absorption ofinsulin using colon-specific nanoparticles co-modified withamphiphilic chitosan derivatives and cell-penetrating
26. peptides. Biomater Sci 2019; 7(4): 1493-506.
27. Farah Benyettou, NawelKaddour, Thirumurugan Prakasam, Gobinda Das, Sudhir Kumar Sharma and Sneha Ann Thomas: *In-vivo* oral insulin delivery *via* covalent organic framework Chem Sci 2021; 12: 6037-6047.
28. Han X, Lu Y, Xie J, Zhang E, Zhu H and Du H: "Zwitterionic micelles efficiently deliver oral insulin without opening tight junctions. Nat Nanotechnol 2020; 15(7): 605–14.
29. Lopes MA, Abrahim BA and Cabral LM: Intestinal absorption of insulin nanoparticles: contribution of M cells. Nanomedicine 2014; 10: 1139-51.
30. Shahbazi MA and Santos HA: Improving oral absorption via drug-loaded nanocarriers: absorption mechanisms, intestinal models and rational fabrication. Currt Drug Metab 2013; 14: 28 56.
31. Yun Y, Cho YW and Park K: Nanoparticles for oral delivery: targeted nanoparticles with peptidic ligands for oral protein delivery. Adv Drug Deliv Rev 2013; 65: 822-32.
32. He C, Yin L and Tang C: Size-dependent absorption mechanism of polymeric nanoparticles for oral delivery of protein drugs. Biomaterials 2012; 33: 8569–78.
33. Bakhru SH, Furtado S and Morello AP: Oral delivery of proteins by biodegradable. nanoparticles. Adv Drug Delivery Rev 2013; 65: 811-21.
34. Han L, Zhao Y and Yin L: Insulin-loaded pH-sensitive hyaluronic acid nanoparticles enhance transcellular delivery. AAPS Pharm Sci Tech 2012; 13: 836-45.
35. Chalasani KB, Russell-Jones GJ and Jain AK: Effective oral delivery of insulin in animal models using vitamin B12-coated dextran nanoparticles. J Control Release 2007; 122:141-50.
36. Chalasani KB, Russell-Jones GJ and Yandrapu SK: A novel vitamin B12 nanosphere conjugate carrier system for peroral delivery of insulin. J Control Release 2007; 117: 421-9.
37. Chuang EY, Lin KJ and Su FY: Calcium depletion-mediated protease inhibition and apical-junctional-complex disassembly via an EGTA-conjugated carrier for oral insulin delivery. J Control Release 2013; 169: 296–305.
38. Su FY, Lin KJ and Sonaje K: Protease inhibition and absorption enhancement by functional nanoparticles for effective oral insulin delivery. Biomaterials 2012; 33: 2801–11.
39. Woitiski CB, Sarmento B and Carvalho RA: Facilitated nanoscale delivery of insulin across intestinal membrane models. Int J Pharm 2011; 412: 123-31.
40. Gao X, Cao Y and Song X: Biodegradable, pH-responsive carboxymethyl cellulose/ poly (acrylic acid) hydrogels for oral insulin delivery. Macromol Biosci 2013; 14: 1-11.

41. Gao X, He C and Xiao C: Biodegradable Ph responsivepolyacrylic acid derivative hydrogels with tunable swelling behavior for oral delivery of insulin. Polymer 2013; 54: 1786-93.
42. Ziv E and Bendayan M: Intestinal absorption of peptides through the enterocytes. Microse Res Tech 2000; 49: 346-352
43. Mukhopadhyay P and Sarkar K. Chakraborty M: Oral insulin delivery by self-assembled chitosan nanoparticles: *in-vitro* and *in-vivo* studies in diabetic animal model. Mater Sci Eng C 2013; 33: 376-82.
44. Jose S. Fangueiro JF and Smitha J: Crosslinked chitosan microspheres for oral delivery of insulin: Taguchi design and *in-vivo* testing. Colloids Surf B 2012; 92: 175-9.
45. Jose S, Fangueiro JF and Smitha J: Predictive modeling of insulin release profile from crosslinked chitosan microspheres. Eur J Med Chem 2013; 60: 249–53.
46. Sung HW, Sonaje K and Liao ZX: pH-Responsive nanoparticles shelled with chitosan for oral delivery of insulin: from mechanism to therapeutic applications. Acc Chem Res 2012; 45: 619-29
47. Kebede A, Singh AK and Rai PK: Controlled synthesis, characterization, and application of iron oxide nanoparticles for oral delivery of insulin. Lasers Med Sci 2013; 28: 579- 87.
48. Qian F, Cui FY and Ding J: Chitosan graft copolymer nanoparticles for oral protein drug delivery: preparation and characterization. Biomacromolecules 2006; 7: 2722-7.
49. Chen MC, Mi FL and Liao ZX: Recent advances in chitosan-based nanoparticles for oral delivery of macromolecules. Adv Drug Deliv Rev 2013; 65: 865-79.
50. Sun Y and Wan A: Preparation of nanoparticles composed of chitosan and its derivatives as delivery systems for macromolecules. J Appl Polym Sci 2007; 105: 552-61.
51. Sonia TA and Sharma CP: *In-vitro* evaluation of N- (2-hydroxy) propyl-3-trimethyl ammonium chitosan for oral insulin delivery. Carbohydr Polym 2011; 84: 103-9.
52. Yin L and Ding J. He C: (Drug permeability and mucoadhesion properties of thiolatedtrimethyl chitosan nanoparticles in oral insulin delivery. Biomaterials 2009; 30: 5691-700.
53. Cui FD, Tao AJ, Cun DM: Preparation of insulin loaded PLGA-Hp55 nanoparticles for oral delivery. J Pharm Sci 2007; 96: 421–7.
54. Liu Y, Kong M and Feng C: Biocompatibility, cellular uptake and biodistribution of the polymeric amphiphilic nanoparticles as oral drug carriers. Colloids Surf B 2013; 103: 345–53.
55. Cui FY, Qian F and Zhao Z: Preparation, characterization, and oral delivery of insulin-loaded carboxylated chitosan grafted poly (methyl methacrylate) nanoparticles. Biomacromolecules 2009; 10: 1253-8.
56. Shelma R and Sharma CP: Submicroparticles composed of amphiphilic chitosan derivatives for oral insulin and curcumin release applications. Colloids Surf B 2011; 88: 722-8.
57. Rekha MR and CP Sharma: Synthesis and evaluation of lauryl succinic chitosan particles towards oral insulin delivery and absorption. J Control Release 2009; 135: 144-151
58. Elsayed A, Al Remawi M, Qinna N, Farouk A and Badwan A: Formulation and characterization of an oilybased system for oral delivery of insulin. European Journal of Pharmaceutics and Biopharmaceutics 2009; 73 (2): 269-79.
59. Ukai H, Iwasa K, Deguchi T, Morishita M, Katsumi H and Yamamoto A: Enhanced intestinal absorption of insulin by capryol 90, a novel absorption enhancer in rats: Implications in oral insulin delivery" Pharmaceutics 2020; 12(5): 1–16.
60. Sharma D and Singh J: Long-term glycemic control and prevention of diabetes complications *in-vivo* using oleic acid-grafted-chitosan zinc-insulin complexes incorporated in thermosensitive copolymer. J Controlled Release 2020; 323: 161–78.
61. Mumuni A. Momoh, Kenechukwu C. Franklin, Chinazom P. Agbo, Calister E. Ugwu, Musiliu O. Adedokun, Ofomata C. Anthony, Omeje E. Chidozie and Augustine N. Okorie: Microemulsion-based approach for oral delivery of insulin: formulation design and characterization Heliyon 2020; 6(3): 03650.
62. Chan AW and Neufeld RJ: Tuneable semi-synthetic network alginate for absorptive encapsulation and controlled release of protein therapeutics. Biomaterials 2010; 31: 9040-7.
63. Sarmento B, Ribeiro A and Veiga F: Alginate/ chitosan nanoparticles are effective for oral insulin delivery. Pharm Res 2007; 24: 2198-206.
64. Sarmento B, Ribeiro AJ and Veiga F: Insulin-loaded nanoparticles are prepared by alginate ionotropic pre-gelation followed by chitosan polyelectrolyte complexation. J Nanosci Nanotechnol 2007; 7: 2833-41.
65. Martins S, Sarmento B and Souto EB: Insulin-loaded alginate microspheres for oral delivery-effect of polysaccharide reinforcement on physicochemical properties and release profile. Carbohydr Polym 2007; 69: 725-731.
66. Reis CP, Ribeiro AJ and Houng S: Nanoparticulate delivery system for insulin: design, characterization and *in-vitro*/ *in-vivo* bioactivity. Eur J Pharm Biopharm 2007; 30: 392-7.
67. Sonia TA and Sharma CP: An overview of natural polymers for oral insulin delivery. Drug Discov Today 2012; 17: 784–92.
68. Reis CP, Veiga FJ, Ribeiro AJ, Neufeld RJ and Damgé C: Nanoparticulate biopolymers deliver insulin orally eliciting pharmacological response. Journal of pharmaceutical sciences 2008; 97(12): 5290-305.
69. Woitiski CB, Neufeld RJ, Veiga F, Carvalho RA and Figueiredo IV: Pharmacological effect of orally delivered insulin facilitated by multilayered stable nanoparticles. Eur J Pharm Sci 2010; 41: 556–563.
70. Li X, Qi J, Xie Y, Zhang X, Hu S and Xu Y: Nanoemulsions coated with alginate/ chitosan as oral insulin delivery systems: preparation, characterization, and hypoglycemic effect in rats. International Journal of Nanomedicine 2013; 8: 23.
71. Hebrard G, Hoffart V, Cardot JM, Subirade M and Beyssac E: Development and characterization of coated microparticles based on whey protein/ alginate using the encapsulator device. Drug Dev Ind Pharm 2013; 39: 126-137.
72. Deat-Laine E Hoffart, V. Garrait G, Jarrige F Cardot JM and Subirade M Beyssac E: Efficacy of mucoadhesive hydrogel microparticles of whey protein and alginate for oral insulin delivery. Pharm Res 2013; 30: 721-734.
73. Huang L, Xin J, Guo Y and Li J: A novel insulin oral delivery system assisted by cationic B-cyclodextrin polymers. J Appl Polym Sci 2010; 115: 1371-1379.
74. Zhang N. J. Li, W. Jiang. C. Ren and J. LIJ. Xin, K. Li: Effective protection and controlled release of insulin by cationic b-cyclodextrin polymers from alginate/ chitosan nanoparticles. Int J Pharm 2010; 3 93: 213-219.

75. Sevil Cikrikci, Mecit HalilOztop and Behic Mert: Development of pH-sensitive alginate/ gum tragacanth-based hydrogels for oral insulin delivery. J Agric Food Chem 2018; Just Accepted Manuscript.
76. Xia Zhou, Hongwel Wu, Rulmin Long, Halwang Huang and Yanhua Xia, Pewang: Oral delivery of insulin with intelligent glucose- responsive switch for blood glucose regulation. J Nanobiotechnology 2020; 18: 96.
77. Lin YH, Chen CT and Liang HF: Novel nanoparticles for oral insulin delivery via the paracellular pathway. Nanotechnology 2007; 18: 1-11.
78. Sonaje K, Chen YJ and Chen HL: Enteric-coated capsules filled with freeze-dried chitosan/ poly (gamma-glutamic acid) nanoparticles for oral insulin delivery. Biomaterials 2010; 31: 3384-94.
79. Sonaje K, Lin KJ and Wang JJ: Self-assembled pH-sensitive nanoparticles: a platform for oral delivery of protein drugs. Adv Funct Mater 2010; 20: 3695-700.
80. 79.Sonaje K, Lin KJ and Wey SP: Biodistribution, pharmacodynamics, and pharmacokinetics of insulin analogs in a rat model: oral delivery using pH-responsive nanoparticles vs. subcutaneous injection. Biomaterials 2010; 31: 6849–58.
81. Lin YH, Sonaje K and Lin KM: Multi-ion-crosslinked nanoparticles with PH responsive characteristics for oral delivery of protein drugs. J Control Release 2008; 132: 141-19.
82. Zhang Z, Shan H and Chen L: Synthesis of pH-responsive starch nanoparticles grafted poly (l-glutamic acid) for insulin-controlled release. Eur Polym J 2013; 49: 2082-91.
83. Minimol PF and Paul W. Sharma CP: PE Gylated starch acetate nanoparticles and its potential use for oral insulin delivery. CarbohydrPolym 2013; 95: 1-8.
84. Lassalle V and Ferreira ML: PLGA based drug delivery systems (DDS) for the sustained release of insulin: insight into the protein/ polyester interactions and the insulin release behavior. J Chem Technol Biotechnol 2010; 85: 1588-96.
85. Yang J, Sun H and Song C: Preparation, characterization and *in-vivo* evaluation of pH-sensitive oral insulin-loaded poly (lactic-co-glycolic acid) nanoparticles. Diabetes, Obesity and Metabolism 2012; 14(4): 358-64.
86. Cui F, Shi K, Zhang L, Tao A and Kawashima Y: Biodegradable nanoparticles loaded with insulin phospholipid complex for oral delivery: preparation, *in-vitro* characterization and *in-vivo* evaluation. Journal of Controlled Release 2006; 114 (2): 242-50.
87. Sara Hosseininasab, RoghiyehPashaei-Asl, Amir Ahmad Khandaghi, Hamid TayefiNasrabadi, KazemNejati-Koshki, Abolfazl Akbarzadeh, Sang Woo Joo, Younes Hanifehpour and Soodabeh Davaran: Synthesis, Characterization and *in-vitro* Studies of PLGA-PEG Nanoparticles for Oral Insulin Delivery. Chem Biol Drug Des 2014; 84: 307–315.
88. Jianyong Sheng, Limei Han, Jing Qin, GeRu, Ruixiang Li, Lihong Wu, Dongqi Cui, Pei Yang, Yuwei He and Jianxin Wang: N-trimethyl Chitosan Chloride-Coated PLGA Nanoparticles Overcoming Multiple Barriers to Oral Insulin Absorption. ACS Appl Mater Interfaces 2015; Just Accepted Manuscript.
89. Wu ZM, Ling L and Zhou LY: Novel preparation of PLGA/ HP55 nanoparticles for oral insulin delivery. Nanoscale Res Lett 2012); 7: 299. DOI: 10.1186/ 1556-276X-7-299.
90. Vauthier C and Bouchemal K: Methods for the preparation and manufacture of polymeric nanoparticles. Pharm Res 2009: 26(5): 1025–1058.
91. Xiong XY, Li YP and Li ZL: Vesicles from pluronic/ poly (lactic acid) block copolymers as new carriers for oral insulin delivery. J Control Release 2007; 120: 11-17.
92. Gebhart CL and Sriadibhatla S. Vinogradov S: Design and formulation of polyplexes based on pluronicpolyethyleneimine conjugates for gene transfer. Bioconjug Chem 2002; 13: 937 -44
93. Iwanaga K. Ono S and Narioka K: Application of surface coated liposomes for oral delivery of peptide effects of coating the liposome's surface on the GI transit of insulin. J Pharm Sci 1999; 88: 248-52.
94. Aragoa MA, Ponchel G and Orecchioni AM: Bioadhesive potential of gliadin nanoparticle systems. Eur J Pharm Sci 2000; 11: 333-41
95. Xiong XY, Tam KC and Gan LH: Hydrolytic degradation of Pluronic F127/ poly (lactic acid) block copolymer nanoparticles. Macromolecules 2004: 37: 3425-30.
96. Ibrahim MA, Fetouhb AI MI and Pferich AG: Stability of insulin during the erosion of poly (lactic acid) and poly (lactic-co-glycolic acid) microspheres. J Control Rel 2005; 106: 241-52.
97. Klier J, Scranton AB and Peppas NA: Self-associating networks of poly (methacrylic acid-y ethylene glycol). Macromolecules 1990; 23 (23): 4944-9.
98. Kavimandan NJ, Losi E and Peppas NA: Novel delivery system based on complexationhydrogels as delivery vehicles for insulin–transferrin conjugates. Biomaterials 2006; 27: 3846–3854.
99. Tang J, Wang Q and Yu Q: A stabilized retro-inversopeptide ligand of transferrin receptor for enhanced liposomebasedhepatocellular carcinoma-targeted drug delivery. Acta Biomater 2019; 83: 379-89.
100. Kohata A, Hashim PK, Okuro K and Aida T: Transferrin-Appended Nanocaplet for Transcellularsi RNA Delivery into Deep Tissues. J Am Chem Soc 2019; 141(7): 2862-6.
101. Kim B and Peppas NA: *In-vitro* release behavior and stability of insulin in complexationhydrogels as oral drug delivery carriers. Int J Pharm 2003; 226: 29–37.
102. Yamagata T, Morishita M, Kavimandan NJ, Nakamura K, Fukuoka Y, Takayama K and Peppas NA: Characterization of insulin protection properties of complexation hydrogels in gastric and intestinal enzyme fluids. J Control Release 2006; 112: 343–349.
103. Wood KM, Stone GM and Peppas NA: Wheat germ agglutinin functionalized complexation hydrogels for oral insulin delivery. Biomacromolecules 2008; 9: 1293-1298.
104. Lochner N, Pittner F, Wirth M and Gabor F: Wheat germ agglutinin binds to the epidermal growth factor receptor of artificial Caco-2 membranes as detected by silver nanoparticle enhanced fluorescence. Pharm Res 2003; 20: 833-839.
105. Carr DA and Peppas NA: Assessment of poly (methacrylic acid-co-N-vinyl pyrrolidone) as a carrier for the oral delivery of therapeutic proteins using Caco-2 and HT29-MTX cell lines. J Biomed Mater Res 2010; 92: 504–512.
106. Sajeesh S and Sharma CP: Mucoadhesive hydrogel microparticles based on poly(methacrylic acid-vinyl pyrrolidone)-chitosan for oral drug delivery. Drug Deliv 2011; 18: 227–235.
107. Shunying Li, Zhiru Chen, Jun Wang, Libiao Yan, Tingting Chen and Qingbing Zeng: Fabrication and characterization of a novel semi-interpenetrating network hydrogel based on sodium carboxymethyl cellulose and poly (methacrylic acid) for oral insulin delivery. Journal of Biomaterials Applications 2020; (0): 1-12.

108. Kato N, Sakai Y and Shibata S: Wide-range control of deswelling time for thermosensitive poly (N isopropyl acrylamide) gel treated by freeze-drying. Macromolecules 2003; 36.
109. Damge C, Socha M and Ubrich N: Poly (epsilon-caprolactone)/ eudragit nanoparticles for oral delivery of aspart-insulin in the treatment of diabetes. J Pharm Sci 2010; 99: 879-89.
110. Damge C, Maincent P and Ubrich N: Oral delivery of insulin associated to polymeric nanoparticles in diabetic rats. J Control Release 2007; 117: 163-70.
111. He P, Liu H and Tang Z: Polyester amide) blend microspheres for oral insulin delivery. Int J Pharm 2013; 455: 259-66.
112. Damge C, Vranckx H, Balschmidt P and Couvreur P: Poly (alkyl cyanoacrylate) nanospheres for oral administration of insulin. J of Pharma Sciences 1997; 86(12): 1403-9.
113. Hou Z, Zhang Z, Xu Z, Zhang H, Tong Z and Leng Y: The stability of insulin-loaded polybutylcyanoacrylate nanoparticles in an oily medium and the hypoglycemic effect in diabetic rats. Yao xuexuebao = Actapharmaceutica Sinica 2005; 40(1): 57-64.
114. Graf A, Rades T and Hook SM: Oral insulin delivery using nanoparticles based on microemulsions with different structure-types: optimization and *in-vivo* evaluation. European J of Pharma Sciences 2009; 37(1): 53-61.
115. Boushra M, Tous S, Fetih G, Xue HY and Wong HL: Development of bi-polymer lipid hybrid nanocarrier (BLN) to improve the entrapment and stability of insulin for efficient oral delivery. J. Drug Deliv Sci Technol 2019; 49: 632–641.
116. Zhang N, Ping Q, Huang G, Xu W and Cheng Y. Han X: Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. International Journal of Pharmaceutics 2006; 327(1-2): 153-9.
117. Fonte P, Nogueira T, Gehm C, Ferreira D and Sarmento B: Chitosan-coated solid lipid nanoparticles enhance the oral absorption of insulin. Drug Delivery and Translational Research 2011; 1(4): 299-308.: 961-963.
118. Yang R, Gao R, Li F, He H and Tang X: The influence of lipid characteristics on the formation, in vitro release, and in vivo absorption of protein-loaded SLN prepared by the double emulsion process. Drug Development and Industrial Pharmacy 2011; 37(2): 139-48.
119. Xu Y, Zheng Y, Wu L, Zhu X, Zhang Z and Huang Y: Novel solid lipid nanoparticle with endosomal escape function for oral delivery of insulin. ACS Applied Materials & Interfaces 2018; 10(11): 9315-24.
120. Jin Y, Song Y, Zhu X, Zhou D, Chen C and Zhang Z: Goblet cell-targeting nanoparticles for oral insulin delivery and the influence of mucus on insulin transport. Biomaterials 2012; 33(5): 1573-82.
121. Pridgen EM, Alexis F, Kuo TT, Levy-Nissenbaum E, Karnik R and Blumberg RS: Transepithelial transport of Fc-targeted nanoparticles by the neonatal fc receptor for oral delivery. Science Translational Medicine 2013; 5(213): 213-167.
122. Joshi HM, Bhumkar DR, Joshi K, Pokharkar V and Sastry M: Gold nanoparticles as carriers for efficient transmucosal insulin delivery. Langmuir 2006; 22(1): 300-5.
123. Bhumkar DR, Joshi HM, Sastry M and Pokharkar VB: Chitosan reduced gold nanoparticles as novel carriers for transmucosal delivery of insulin. Pharm Res 2007; 24(8): 141.

How to cite this article:
Chaudhary HK, Vandana and Malik A: Concerns and limitations of materials for oral delivery of insulin. Int J Pharm Sci & Res 2022; 13(9): 3357-74. doi: 10.13040/IJPSR.0975-8232.13(9).3357-74.