http://doi.org/10.25130/tjphs.2025.19.2.6.60.76

IRAQI Academic Scientific Journals

Tikrit Journal of Pharmaceutical Sciences

ISSN: 1815-2716 (print) -- ISSN: 2664-231X (online)

Journal Home Page: https://tjphs.tu.edu.iq -- Email: tjops@tu.edu.iq

TJPHS

Comparison of the Pros and Cons of pH-Responsive Systems for Oral Insulin Delivery: A Concise Review

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Keywords:
Oral Insulin, pH responsive carriers, Hydrogel, Nanoparticles, Diabetes mellitus.

Article history:
-Received: 27/07/2025
-Received in revised: 21/08/2025
-Accepted: 05/01/2026
-Available online: 16/01/2026

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Citation:
Alhazza H J, Okab A K, Alkufi H K. Comparison of the Pros and Cons of pH-Responsive Systems for Oral Insulin Delivery: A Concise Review. Tikrit Journal of Pharmaceutical Sciences. 2025; 19(2):60-76.
http://doi.org/10.25130/tjphs.2025.19.2.6.60.76

Abstract

Oral drug delivery is regarded as the most favored method of treatment due to its elevated patient compliance and reduced invasiveness. The oral route of administration of therapeutic proteins such as vaccines, antigens and hormones (insulin), compared to other routes, requires delivery systems that can overcome glitches in therapeutic proteins optimal utilization such as extensive first-pass hepatic metabolism, destruction in the gastrointestinal tract, large molecule size and poor penetration. Therefore, pH-responsive carriers for the delivery of insulin orally are regarded to be one of the most promising options. Insulin is now available in parenteral dose form, which can be administered mainly by subcutaneous injections. Subcutaneous administration method is linked with a number of complications that might impair patients' compliance. Oral administration of insulin is not currently feasible due to a number of problems that are associated with the structure of insulin and the architecture of the gastrointestinal system. Insulin is a peptide that, when oral administration occurs, has a tendency to be rendered inactive through the process of destruction that is accomplished by the enzymes and acids of the stomach. Therefore, the pH-responsive carriers make an effort to bypass the stomach. This allows for insulin release and subsequent absorption in its unaltered form within the intestine by aid of absorption enhancers. This review will discuss the progress made in the field of pH-responsive systems, with a particular focus on oral insulin delivery. It provides a comprehensive comparison of pH-responsive systems with other delivery systems from various aspects, such as formulation, insulin loading, and large-scale manufacturing, as well as the future prospects for oral insulin delivery. It also discusses the challenges that may be faced in scaling up production and offers our perspective on the clinical translation of *in vitro* findings into commercial products.

مقارنة بين إيجابيات وسلبيات أنظمة الاستجابة للأس الهيدروجيني لتوصيل الإنسولين عن طريق الفم: مراجعة مختصرة

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الخلاصة

يُعتبر توصيل الأدوية عن طريق الفم الطريقة المفضلة للعلاج نظرًا للامتثال العالي للمرضى وقلة التدخل الجراحي. يتطلب الطريق الفموي لإعطاء البروتينات العلاجية مثل اللقاحات والمواد المستضدية والهرمونات (الإنسولين)، مقارنة بالطرق الأخرى، أنظمة توصيل يمكنها التغلب على المشكلات في الاستخدام الأمثل للبروتينات العلاجية مثل الاستقلاب الكبدي الكامل خلال المرور الأول في الكبد، والتدمير في الجهاز الهضمي، وكبر حجم الجزيئات، وضعف النفاذية. لذلك، تُعد الحاملات المستجيبة للأس الهيدروجيني لتوصيل الإنسولين عن طريق الفم واحدة من أكثر الخيارات الواعدة. يتوفر الإنسولين الآن في شكل جرعات وريدية يمكن إعطاؤها أساسًا عن طريق الحقن تحت الجلد. طريقة الإعطاء تحت الجلد مرتبطة بعدد من المضاعفات التي قد تؤثر على التزام المرضى بالعلاج. إعطاء الأنسولين بدون تعديل عن طريق الفم غير ممكن حاليًا بسبب عدد من المشكلات المرتبطة ببنية الأنسولين وبنية الجهاز الهضمي. الأنسولين هو ببتيد، وعند إعطائه عن طريق الفم، يميل إلى أن يفقد فعاليته بسبب عملية التحلل التي تقوم بها إنزيمات وأحماض المعدة. لذلك، فإن الحوامل المستجيبة للأس الهيدروجيني تسعى لتجاوز المعدة. هذا يسمح بتحرير الأنسولين وامتصاصه لاحقًا بصيغته غير المتغيرة داخل الأمعاء بمساعدة معززات الامتصاص. ستناقش هذه المراجعة التقدم المحرز في مجال الأنظمة المستجيبة للأس الهيدروجيني، مع التركيز بشكل خاص على توصيل الأنسولين عن طريق الفم ويوفر مقارنة شاملة بين الأنظمة المختلفة من جوانب عدة مثل التركيب والمكونات والقابلية على حمل كمية الانسولين والتصنيع على شكل واسع فضلا عن الافاق المستقبلية. كما يناقش التحديات التي تواجه التصنيع ويقدم وجهة نظر حول تحويل النتائج او التجارب المختبرية الى منتج تجاري ناجح.

الكلمات المفتاحية: الانسولين الفموي, الحوامل المستجيبة للأس الهيدروجيني, الجسيمات النانوية, مرض السكري.

Introduction

Diabetes mellitus (DM), is a chronic endocrine disorder, is marked by high blood sugar levels due to reduced insulin production from impaired or failed pancreatic function and/or decreased cellular response to insulin [1][2][3]. According to the International Diabetes Federation, the global prevalence of diabetes is expected to become 643 million adults by 2030, compared to 537 million in 2021[4]. According to the World Health Organization, the serious complications and prevalence associated with diabetes result in more than three million deaths annually worldwide [5]. DM is usually categorized into the two types: type 1 mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM results from insufficient or absent insulin production due to pancreatic beta cell dysfunction, while T2DM is characterized by reduced insulin sensitivity in cells. Both conditions disrupt blood glucose balance, leading to hyperglycemia [6]. Persistent high blood sugar levels can cause long-term complications such as cardiovascular issues, stroke, kidney damage, vision loss, nerve damage, and lower limb amputations [6][7][8]. In contrast, T2DM develops gradually due to a progressive decline in insulin production and sensitivity, requiring insulin therapy over time. Symptoms include dry skin, frequent urination, light sensitivity, fatigue, blurred vision, and excessive thirst [9]. The primary therapy objectives for diabetes include eradicate hyperglycemia and its related consequences. Since its initial discovery in 1921, insulin has served as the fundamental treatment for diabetes, particularly for individuals with T1DM [10]. Patients with T1DM experience either an absence or a decrease in insulin secretion from the pancreas, necessitating numerous injections of both rapid acting and long acting insulin to replicate postprandial and baseline blood glucose levels [6]. In this review, we critically evaluate the advantages and disadvantages of pH-responsive systems in the context of oral insulin delivery. We identify the advantages of pH-responsive systems as the next-generation delivery system compared to standard delivery methods; we discuss the current obstacles related to their clinical and industrial translation. We also explain critical

formulation, such as hydrogels, polymeric nanoparticles, mesoporous silica nanoparticles pH-responsive cationic polymeric micelles and cellulose microspheres as well as the possibility of enhancing pharmacokinetic properties suitable for use as an oral insulin delivery system. In addition, we explore the uses and compare it with other delivery systems. The essence of this discussion is to attempt to develop a vision of how pH-responsive systems, using only the essential components, can provide better oral insulin delivery. In addition to pH responsive carriers, several approaches are available to address problem of poor oral bioavailability of insulin as shown in figure 1.

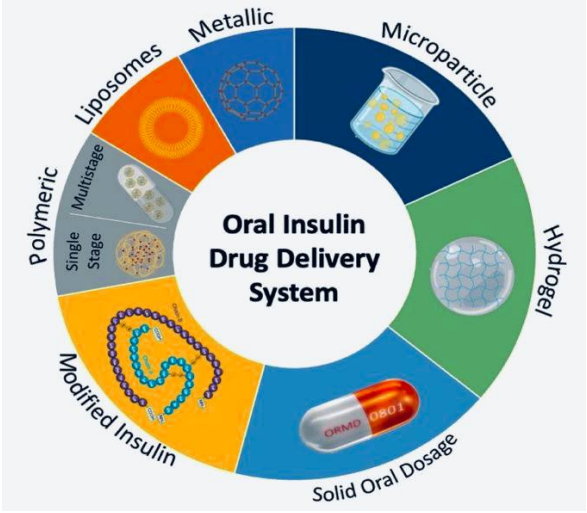

Figure 1: approaches of oral insulin delivery systems.

Routes of Insulin Administrations

Insulin therapy could be administered to patients by numerous routes, including parenteral, pulmonary, and nasal. The primary concern with these systemic ways is that only a limited fraction of insulin can effectively reach the liver for its physiological function. The retention of insulin in peripheral circulation may result in peripheral resistance to insulin and immunogenicity. Hyperinsulinemia may arise when administered insulin acts on inappropriate targets, resulting in hypertension, heart disease, weight gain, and peripheral oedema [11], [12]. Subcutaneous injections remain the predominant method for the routine administration of insulin. This approach presents multiple drawbacks, such as poor patient adherence due to discomfort, needle aversion, hypoglycemia incidents, and allergic responses [13].In comparison to alternative routes, the oral administration of insulin presents multiple advantages over other systemic delivery methods. For instance, the local pain, discomfort, irritation, needle stick injuries, and the danger of skin infections like *Staphylococcus aureus* and *Mycobacteria chelonae* associated with injections are nonexistent [14]. The oral administration of insulin enhances portal drug levels and reduces periphery hyperinsulinemia, which has been linked with neuropathy and retinopathy in alternative routes of delivery [15]. The oral administration can enhance health outcomes for diabetes management by enhancing patients' living conditions.

Oral Insulin Therapy

Researchers have exerted significant efforts to create oral insulin preparations since the initial finding of insulin by Best and Banting in 1921[16]. The initial attempt to develop oral insulin occurred in the year that followed. Throughout a week of repeated oral administration of progressively dosed insulin formulations, the patient exhibited no improvement in metabolic function [17]. Numerous clinical studies of oral insulin occurred from 2001 to 2019. Despite many businesses discontinuing the development of oral insulin due to clinical trial challenges, others, including Emisphere in the US, Diabetology in the UK, and Oramed in Palestine [18]. In 2001, Emisphere obtained FDA approval to conduct a Phase I clinical trial for its initial oral insulin formulation. An alternative insulin oral formulation from Emisphere completed phase II clinical trials five years later. Nevertheless, the outcomes were insufficient, as substantial differences were noted among the control and intervention groups. This was primarily attributable to the restricted sample size of simply eight patients. In 2014, Oramed's ORMD-0801 obtained FDA approval to Phase III clinical studies. The

sample size comprised 710 diabetic patients. Nonetheless, the outcomes remained unsatisfactory. No significant improvement in glycemic control was noted in participants administered oral insulin compared to those receiving placebo following 26 weeks of treatment [17], [18]. The major issue for oral product development is the GI barriers according to many researches [7], [19]. Due to the significant need for oral administration in clinical applications, numerous studies have concentrated on creating innovative technologies that overcome gastrointestinal barriers of insulin, including enteric coating, inhibitors of enzymes, permeability enhancers, nanoparticles, and intestinal micro devices. Several novel technologies have been invented during clinical trials and are currently available on the market as shown in **Table** 1 [20], [21].

Table 2: Oral Insulin Delivery Systems Undergoing Clinical Trials

Product Name	Manufacturer	Technology	Status
IN-105	Biocon	Insulin conjucated with PEG	Phase II
ORA2	BOWS Pharmaceuticals	Capsule containing insulin in dextran	Phase II in T2DM
Capsulin	Diabetology	Axcess, enteric coated capsule filled with mixture of insulin and absorption enhancer.	Phase II a in T1DM and phase II in T2DM
NN1953; NN1954	Novo Nordisk	Tablet of long-acting insulin	Phase I in T1DM and T2DM
ORMD-0801	Oramed	Enteric coated capsule containing insulin and adjuvants	Phase III

The Barriers to The Oral Absorption of Insulin

Numerous issues limit the advancement of oral insulin development, including instability in the gastrointestinal tract, inadequate permeability across intestinal epithelia, and challenges in formulation development (**Figure** 2). The physiological obstacles are significant impediments to the oral absorption of insulin, due to the inherent characteristics of the gastrointestinal tract, which primarily facilitates food digestion and nutrient absorption. Following oral delivery, medicines are initially exposed to gastric juices in the stomach before progressing to the small intestine, where the majority of drug absorption occurs. Nonetheless, the environments of the stomach and intestines differ significantly, encompassing pH, enzymes, mucus, and epithelial permeability, all of which affect the stability and absorption of insulin.

The pH varies from the stomach to the intestine, transitioning from the acidic range of 1.2–3.0 in the stomach to a slightly alkaline range of 6.5–8.0 within the intestinal wall. The alteration of acid levels may lead to pH-induced combustion and dehydrogenation to insulin similar to transcription factor compounds [20]. Insulin is highly vulnerable to numerous proteolytic enzymes, involving luminal enzymes from intestinal and pancreatic secretions, bacterial enzymes in the colon, and mucosal enzymes, all of which affect its stability [21]. Another physiological factor is mucus, a sticky and viscoelastic gel layer that covers the entire gastrointestinal tract. The mucus presents several obstacles to the passage of insulin throughout the submucosal tissue [20]. In addition to physiological barriers, formulation presents a significant challenge in the development of commercial oral insulin products. The stability of insulin, both chemically and physically, is paramount in formulation development, which

seeks to ensure its stability during manufacturing, transportation, storage, and administration [22].

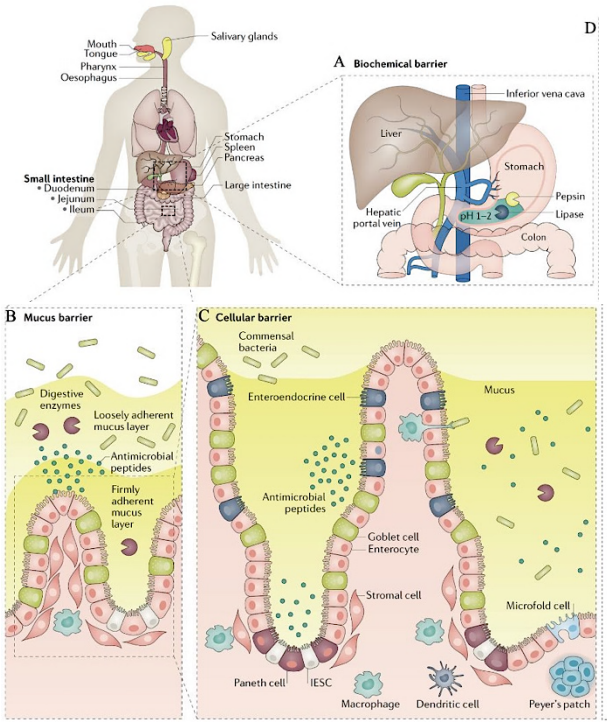

Figure 2: Oral insulin development challenges **(A)** Biochemical barrier: The interplay of acidic and alkaline environments, along with diverse enzymes in the gastrointestinal tract. **(B)** The mucus barrier. **(C)** The epithelial barrier regulates nutrient transfer between the intestinal lumen and the lymphatic system or bloodstream.

Approaches for Oral Insulin Delivery

Over the previous decades, scientists try to overcome the limitations of oral delivery of insulin by using different technique, methods, carrier systems, excipients, chemical modification, coatings and the pH responsive oral insulin delivery system.

pH-Responsive Approaches for Oral Insulin Delivery

The hostile stomach environment is the first biological barrier that oral insulin delivery (ODS) encounter when they target the small intestine. Stomach acid (pH 1.0-2.5) can denature chemicals that are susceptible to acid, and the digestive enzymes break down the payload fast. Therefore, when targeting the small intestine, it is vital so that drugs remain stable when passed through the stomach. A crucial method for intestinal targeting is pH dependency, which is necessary due to the large pH gradient along the gastro-intestinal tract. ODS are said to be pH-responsive if they modify their interaction with their environment in response to variations in pH [23]. It is common practice to formulate these pH-responsive polymer systems using a mix of polycations and polyanions. Solubility and subsequent expansion at a targeted pH determine the release mechanism. One typical component for the release of medications that target the intestines is calcium alginate. It can withstand the acidic conditions of the stomach but breaks down in the neutral intestine [24]. These carriers including hydrogel, polymeric nanoparticles, micelles, Mesoporous silica nanoparticles and microspheres.

A- Hydrogels

With the ability to expand under physiological enviroment and retain water multiple times their dry weight, hydrogels are a type of hydrophilic polymer composed of three-dimensional viscoelastic networks. Hydrogels have the potential to be utilized as biomaterials due to their unique properties, including their high water content, supple and elastic texture, and minimal adhesion force with biological fluids or water. The controlled dissolution, preservation of labile drugs, and regulation of molecular release are all made possible by hydrogels' distinctive physical characteristics [25]. With a size range of 10-1000 nm, hydrogel is a nanomaterial. Hydrogel carriers for the oral administration of insulin have been developed using naturally occurring polymers such as chitosan, cellulose, starch, pectin, and psyllium. Because of their mucoadhesive qualities, hydrogels are considered safe oral medication delivery vehicles. Medications may take longer to be absorbed if this happens. Hydrogels have the ability to shield the injected medications from enzymatic breakdown, which is an additional perk of employing them as oral drug delivery vehicles. Oral insulin is delivered by means of PH-responsive polymeric hydrogels composed of

cross-linked poly (ethylene glycol) and poly (methacrylic acid) [26]. The rapid secretion of insulin in the intestines is a result of the cross-linking properties of these hydrogels, which are dependent on the pH. They are highly effective at loading insulin and exhibit mucoadhesive properties; nevertheless, they do not compromise the integrity of the intestinal epithelial barrier as shown in **Figure** 3. When it comes to crosslinking agents, those with hydrophobic groups tend to collapse in water, reducing hydrogel swelling, whereas those with hydrophilic groups can generate a higher degree of swelling. When the materials swell at a certain pH, the drugs are released from pH-responsive hydrogels [27]. Hydrogels can be tuned for prolonged macromolecule release by altering their hydrodynamic radius, which is usually 5 to 100 nm with inflation. **Figure** 4 shows acid-sensitive bonds that break to release molecules attached to the backbone and ionizable groups that change solubility and shape in response to ambient pH. The main pH-responsive hydrogels are anionic and cationic.

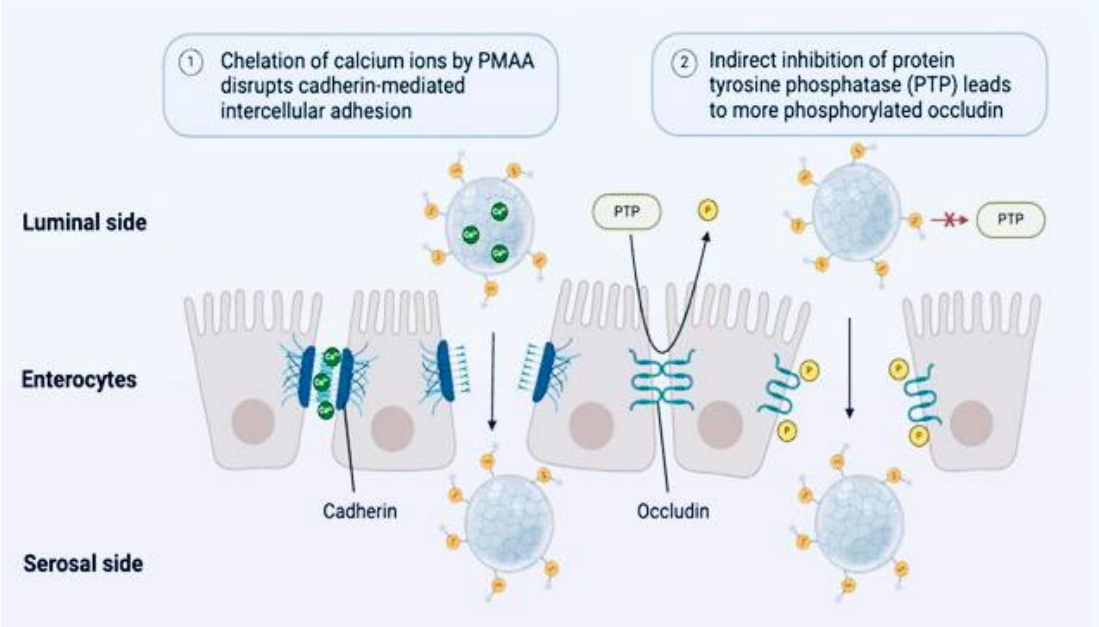

Figure 3: Opening of tight junction through thiolization of polymethacrylic acid (PMAA -chitosan-PEG (PCP) hydrogel.

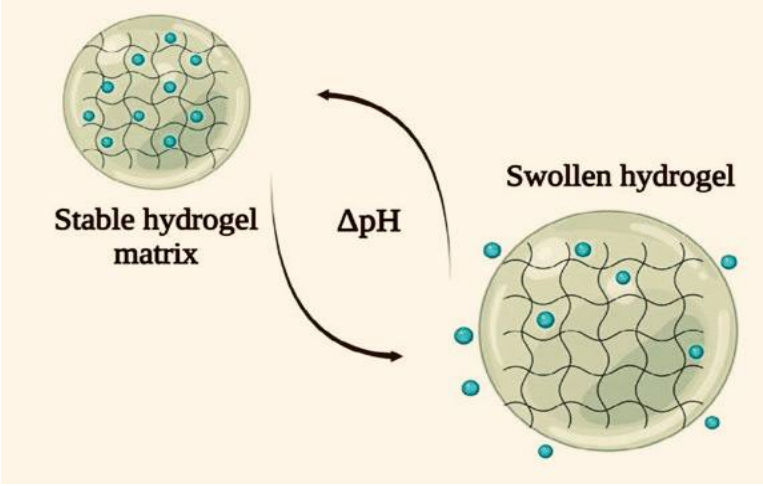

Figure 4: Swelling/ de-swelling of hydrogel matrix loaded with drug with response to pH change.

At pH levels higher than the polymer network's pKa, anionic hydrogels become ionized and swell [30]. Intragastric drug delivery systems shield medications from stomach acid and

denaturation at low pH while releasing them into designated areas, like the colon and upper small intestine. Solution ionic strength impacts hydrogel swelling. Since the hydrogel is deflated, ionic strength does not affect swelling below pKa. At pH values above the polymer network's pKa, anionic hydrogels swell less with ionic strength. Ion shielding minimizes negative carboxylic acid group electrostatic repulsion as ionic strength increases. Cationic hydrogels ionize when their pH drops below the polymer network's pKa, unlike anionic ones. Cationic hydrogels help stomach or cell-released drugs [31]. Because of the amino acid groups, cationic polymers have a high water solubility at acidic pH and a low one at neutral pH. To ensure that medications remain stable in the mouth (pH 5.8–7.4) before being released into the stomach (pH 1-3.5), oral delivery devices make use of cationic polymers. Because of their low solubility at neutral pH, cationic polymers are frequently employed in taste-masking formulations to prevent the release of medicines [32].

Table 2 summarizes the systems used as examples.

	Polymer	Target site	Test drug	References
Anionic	poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)]	Small intestine	Insulin	[33]
Cationic	Chitosan	Small intestine	Insulin	[34]

Poly(anhydride ester) and poly(acrylic acid) hydrogels were created by Demirdirek and Uhrich to regulate insulin and salicylic acid release from the hydrogel matrix. Hydrogels produced 90% insulin in a basic environment and 4% in an acidic one. This research sheds light on gastric pH-resistant pH-dependent oral insulin administration [35]. Research in Farya's lab centered on developing nanocomposites and pH-responsive hydrogels for the release of insulin. Acrylic acid and methacrylic acid monomers exhibited different pH-responsive behavior because to the different amounts of crosslinkers. In order to shield insulin from stomach acids and maximize intestinal release, swelling studies showed a small expansion at acidic pH and a large expansion at physiological pH (7.4). Variations in the concentrations of monomers and crosslinkers had a significant impact on the swelling. A higher concentration of the crosslinker resulted in less edema because the crosslinking density was higher. Pepsin in gastric juice was unable to breakdown insulin in studies involving insulin release. [36]. Zhang et al. developed an insulin-encapsulated nano hydrogel utilizing O-carboxymethyl chitosan and sodium alginate in an independent investigation. This nano-system exhibited a bioavailability of 6.5%, ensuring pH-specific intestinal release of insulin for more than 12 hours in rats with type 1 diabetes [37]. An oral insulin administration method based on microalgae was created in the Ren research by cross-linking an insulin delivery system based on Chlorella vulgaris (CV) with sodium alginate (ALG) [38]. Bypassing the GI tract and protecting insulin from acidic stomach environment is possible using CV-Insulin-ALG, which also allows for pH-responsive medication release in the intestines. CV-Insulin-ALG may have a role in both endocytosis by M cells and macrophages and direct insulin release from the delivery system,

the two pathways that are involved in insulin absorption [39]. In a mouse model of type 1 diabetes generated by streptozotocin (STZ), CV-Insulin-ALG had a longer-lasting hypoglycemic effect than direct insulin administration while causing no harm to the intestines. In addition, type 2 diabetic mice showed an improvement in insulin sensitivity after receiving long-term oral treatment of the carrier CV-ALG, which improved gut microbiota disorder and dramatically raised the abundance of probiotic Akkermansia. Following oral administration, microalgal insulin delivery devices demonstrated excellent biodegradability and biosafety by degrading and being metabolized in the intestines. An oral insulin delivery system that uses microalgal biomaterials is an efficient, natural, and multipurpose option [40].

B- Polymeric nanoparticles.

Taking into consideration the mucosal adhesion characteristics of PDM and the pH responsiveness of hyaluronic acid (HA), Wang created three HA-PDM nano-delivery systems for insulin. The HA molecules used in these systems had different molecular weights. All three varieties of nanoparticles have similarly sized particles and negatively charged surfaces. A medication loading of 11% (w/w) was considered optimal. At a pH of 1.2, the insulin release was 22%, and at a pH of 7.4, it was 63.23%. Oral administration was followed by pharmacodynamic and pharmacokinetic investigations in diabetic rats. With a relative bioavailability of 14.62%, all three formulations showed a long-lasting hypoglycemic impact. In conclusion, there is great promise for industrial advancement with these simple, environmentally benign, pH-responsive, and mucoadhesive nanoparticles. Insulin delivery via oral administration is supported by initial findings offered by this investigation [41]. Sung developed a method for the enzymatic assembly of hydrophilic chitosan (CS) and poly (γ-glutamic acid) (γ-PGA) nanoparticles to facilitate the paracellular route of oral delivery of hydrophilic macromolecules. There have been studies in the literature about the preparation of NPs using the ionic gelation of CS with tripolyphosphate sodium (TPP) or poly (acrylic acid) (PAA) to increase the intestinal absorption of protein molecules. The research details the pH-responsive characteristics of CS nanoparticles and how they promote the reversible opening of epithelial tight junctions (TJs). Subsequently, as illustrated in Figure 5, in vivo findings suggest that NPs containing a high concentration of CS may adhere to the intestinal mucosa, remain there for an extended period, and subsequently open epithelial transepithelial junctions if administered orally. Furthermore, we discuss the oral biodistribution, function, and efficacy of the insulin-loaded NPs. The blood glucose levels of diabetic rats were found to decline significantly and remain rather stable for an extra six hours following the oral administration of insulin-loaded NP, which took four hours. Everything said before demonstrates that our insulin-loaded NPs effectively reduce blood sugar levels [42].

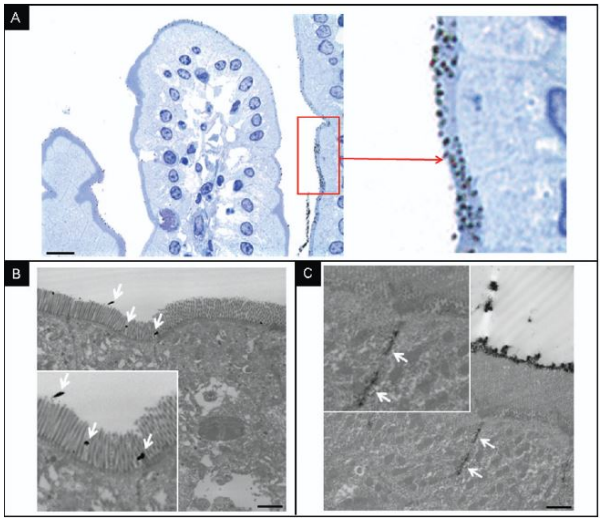

Figure 5: (A) Photomicrographs and (B) TEM micrographs of silver-enhanced intestinal sections showing the mucoadhesion and infiltration of quantum-dot-labeled CS NPs (black dots) and (C) permeation of lanthanum through the opened paracellular space.

C- Mesoporous silica nanoparticles (MSNs).

MSNs have a lot of great physical and chemical qualities that make them a potential drug release mechanism. These include highly modifiable surface properties, a large specific

surface area, variable pore size, good biocompatibility, and degradability as shown in **Figure** 6 [43]. Furthermore, polymers that can adjust their size and structure in response to variations in pH have garnered a lot of interest for use in smart drug release systems. A pH-responsive drug carrier for drug release is unique in that it may be used to provide intelligent drug release by adjusting the medium's pH value. The hydrothermal synthesis of pH-responsive cylindrical MSN has demonstrated the promise of this new formulation for insulin orally delivered. A pH-responsive self-regulating release platform was built for insulin administration by the coordination of metal ions. They developed a method to create a controlled medication release system by utilizing the copper metal ion as an intermediary between the amino group modified mesoporous silica and insulin [44]. An MSN that is organized in response to stimuli is the subject of the present study because of its potential to improve drug loading and surface modification of stimuli-responsive polymers on mesoporous silica. In addition to preventing the medication from being released too early during delivery, these stimuli-responsive "on-offs" can start the drug's release by stimulating its pH, which is caused by changes in its physical and chemical structure. pH-sensitive mesoporous silica nanoparticles were synthesized by surface modification of insulin-loaded mesoporous silica with hydroxypropyl methylcellulose phthalate. Insulin oral release and high-drug loading were the goals of MSN's design. The insulin-loading device that was created included mesoporous silica (SBA-15) and pH-sensitive enteric-coated material (HP55). Because SGF prevented the breakdown of insulin by pepsin in gastric juice, the cumulative release in SIF was double that of SGF, according to the results of the insulin release experiment. Fick diffusion was also used in both the solid-state and liquid-phase release of 15% HP55@SBA-15/INS. The MSN showed no cytotoxicity at concentrations between 6.25 and 100 mg/mL, proving that they may be utilized as an insulin delivery vehicle [45].

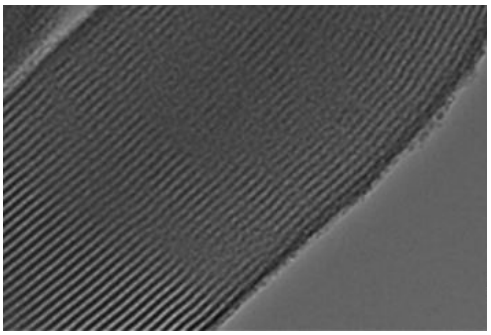

Figure 6: TEM images of mesoporous silica SBA-15.

D- pH responsive cationic polymeric micelles (PCPMs)

Because of insulin's great delivery efficacy and PCPMs' appropriate pH-triggered release feature, they are the most researched and used insulin carriers for targeted delivery and regulated release. By increasing intestinal permeability and improving insulin delivery efficiency, intelligent PCPMs shield insulin from burst release and enzymatic destruction in gastric juice. Insulin is then released at the intestinal environment. As demonstrated in Figure 7, the nanoparticles were able to load and safeguard insulin within the micellar core even when subjected to acidic conditions. The drug loading capacity and pH-triggered release feature are both optimized by this form of random hydrophobic/pH-sensitive structure, in comparison to the particular structure control. Surrounding the surface of the self-assembled micelles, the hydrophilic and pH-sensitive poly[2-(diethylamino)ethyl methacrylate (PAEMA) segments provide a steric protective layer that enhances the stability of the micelles. The amine residues of PAEMA can undergo sharp protonation in an acidic environment, such as the stomach, creating a positively charged surface. This surface then serves the mucoadhesion function, which improves medication permeability by opening the tight junction in the intestines. Micelles loaded with insulin showed pH-dependent insulin release patterns in vitro. The release rate of loaded insulin rose as the ratio of MAA increased; nevertheless, in simulated gastric fluid, less

than 20% of the insulin content released over 2 hours, whereas in simulated intestinal fluid, approximately 60% of the insulin content released within 10 hours. The results showed that PCPMs made of co-polymer could be a good vehicle for insulin delivery when taken orally.

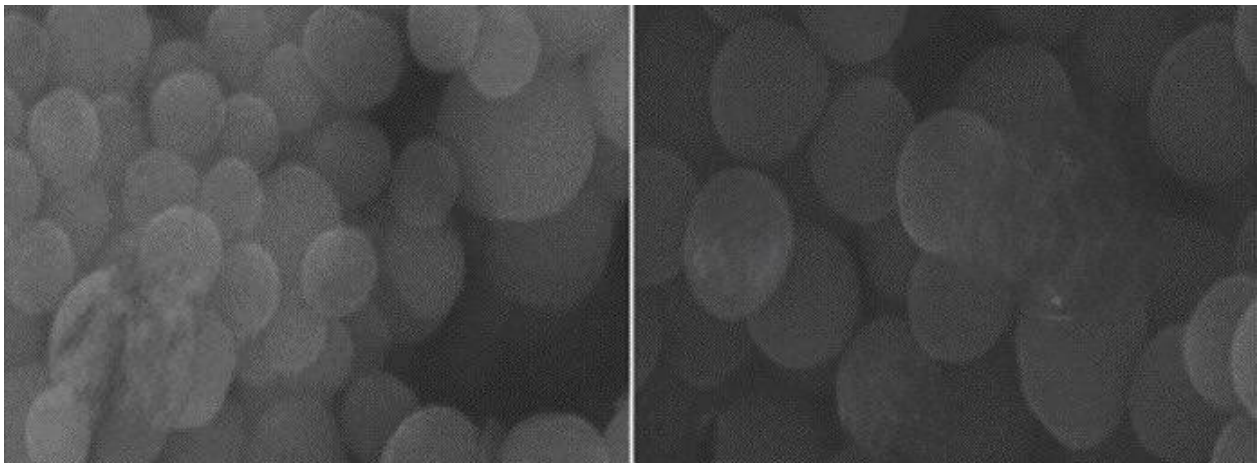

Figure 7: SEM images of Insulin-loaded PCPMs.

By increasing intestinal permeability and insulin delivery efficiency, intelligent PCPMs safeguard insulin against gastric juice burst release and enzymatic destruction. The pancreas secretes insulin. Despite the presence of acid, the micellar core was protected when insulin was injected into it by nanoparticles. The drug loading and pH-triggered release are both optimized by this random hydrophobic/pH-sensitive structure in comparison to the structural control. PAEMA segments provide a steric barrier and stabilize micelles. The amine residues of PAEMA undergo strong protonation in stomach acid, resulting in a positively charged surface. The mucoadhesion process improves medication permeability by opening the tight junction in the intestines. In vitro insulin release by insulin-loaded micelles was pH-dependent. Insulin content released in simulated gastric fluid over 2 hours was less than 20%, whereas in intestinal fluid over 10 hours it increased to 60%, with an increasing MAA ratio. The results raised the possibility of using co-polymer PCPMs for oral insulin administration[46].

E- Cellulose Microspheres (CMs).

Due to its high porosity, hydrophilicity, biocompatibility, and remarkable modifiability potential, cellulose microspheres (CMs) have been extensively studied. It is reasonable to employ cellulose-based microspheres as a medication carrier as shown in **Figure** 8. In spite of its shortcomings compared to the nanometer system, the microsphere method has the benefit of regulating the quantity of stomach-released insulin, which shields insulin from the stomach's hostile environment. The sol-gel approach makes it easier to manufacture CMs using a green solvent, which is an aqueous solution of sodium hydroxide and urea. Insulin loading and regulated release are made possible by cellulose-based microspheres, which have a high porosity, an acceptable specific surface area, and are hydrophilic. Furthermore, by adjusting the interfacial microstructure of cellulose-based microspheres—including pore size and particle size—in line with the insulin's structure and physicochemical properties, high-performance oral insulin carriers can be designed, resulting in improved insulin bioavailability. The structure of the insulin carrier can be maintained throughout continuous in-body release of cellulose-based microspheres loaded with insulin since cellulose is neither digested nor biodegradable in humans. Evidence from *in vitro* release tests

shows that insulin released 48.87 % in artificial gastric fluid and 85.12 % in artificial intestinal fluid. Circular dichroism analysis shows that the enzyme was able to load and release insulin while maintaining its secondary structural stability. Carboxylated cellulose microspheres (CCMs) were shown to be non-cytotoxic, according to cell viability testing. These findings suggested that the proposed CCMs may be used for oral insulin administration, as the encapsulation of insulin into them improved its oral bioactivity and absorption [47].

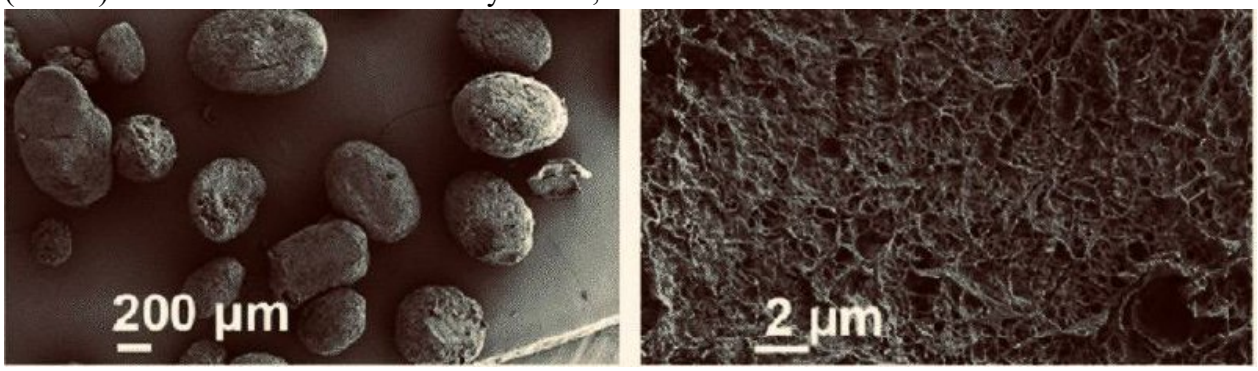

Figure 8: Insulin -carboxylated cellulose microspheres (CCMs).

Combination strategies

A new study found that physical combinations of cell-penetrating peptides (CPPs), like oligoarginines, significantly improve insulin absorption in the intestines. For the purpose of increasing macromolecule oral absorption, the noncovalent CPP method is employed. Using P(MAA-g-EG) hydrogel to protect encapsulated insulin in the stomach and allow for its broad release in the small intestine improved the intestinal absorption of therapeutic peptides and proteins. In addition to exhibiting mucoadhesive properties in the intestines, P(MAA-g-EG) hydrogel microparticles inhibit proteolytic enzymes in the gastrointestinal tract. Combining P(MAA-g-EG) hydro-gel carriers, which help with drug protection and controlled release, with CPP, which has a permeation stimulatory effect, could be a good strategy for insulin delivery by mouth. [48].

Discussion

Research into pH-responsive oral drug delivery systems has grown in stature in recent decades, thanks to notable developments in the field. Vast amounts of experimental data have laid a solid groundwork, but there is still plenty of room for improvement, particularly in terms of improving delivery specificity and translating that into clinical use. If we want to put this theory into practice, we need drug delivery devices that can detect changes in pH, release drugs selectively to specific sites, and perform other desirable multifunctionalities. In addition, there is still a long way to go until we can easily, cheaply, and precisely synthesize materials with precisely defined structure, size, form, and chemical properties. Biocompatible and biodegradable nanostructured materials are crucial for practical applications, yet there is a dearth of data on innovative oral drug delivery systems that respond to pH. Biomedical researchers are currently examining the chemical and thermal stability of inorganic materials such as carbon, rare earth oxides and fluorides, metal oxides, silica, and noble metals. These materials aren't very useful in living organisms because they don't break down easily. Oral administration of novel pH-responsive, biodegradable nanostructured inorganic materials showed promise due to their great biocompatibility and lack of toxicity. Progress is needed to control size, structure, morphology, and drug loading. Biodegradability, dispersion routes, and in vivo biotoxicity require further investigation for potential future uses. Further research is needed to fully understand the processes inside the physiological environment of pH-

responsive carriers, with an emphasis on conducting in vivo studies to improve their therapeutic applications. Investigating the interactions between pH-responsive carriers and drug molecules will hold substantial theoretical and practical importance for the development of innovative oral drug delivery systems, enabling controlled drug release, improved drug loading capacity, and further examination of potential mechanisms. **Table 3** summarize the main differences among the most important strategies.

Table 3: Comparison of the pH Responsive carriers

pH Responsive system	**Hydrogel**	**Polymeric nanoparticles**	**Mesoporous silica nanoparticles**	**pH-responsive cationic polymeric micelles**	**Cellulose microspheres**
Advantages	The controlled dissolution, preservation of labile drugs, and regulation of molecular release**,** effective at loading insulin, biocompatible, biodegradable, controlled release and high water content.	High stability, targeted delivery potential, tunable properties and increased bioavailability.	High loading capacity, excellent protection for insulin, tunable pore size, biocompatibility and easy to functionalize.	Enhanced absorption, protection of insulin and good solubility.	Biocompatible, porous structure, and green synthesis.
Disadvantages	Mechanical stability issues, difficult to scale up and potential for burst release.	Low loading capacity, potential for toxicity and lack of stability in some cases	Concerns about long-term toxicity and challenging to achieve controlled release without extensive modification.	Lower stability, potential for strong interaction with mucus and potential cytotoxicity	Larger size may lead to lower bioavailability and uncontrolled release.
Clinical stage	Still in the preclinical or early-stage clinical trial (Phase I) stage.	The majority are in the preclinical stage. Some may be entering Phase I or Phase II trials, but they are not yet in widespread clinical use for	Are a newer class of materials. The vast majority of research for oral insulin delivery is in the preclinical stage. There are ongoing studies to evaluate their safety and	Research is largely in the preclinical stage. The focus is on optimizing the balance between stability, charge, and release to achieve a	Most research is in the preclinical stage. While cellulose-based materials are widely used in pharmaceuticals, the specific application of cellulose microspheres for oral insulin

		this specific application.	efficacy in animal models.	therapeutically relevant effect.	delivery is a newer field of research.

Conclusion

The efficacy of oral insulin in transporting through the challenging gastrointestinal environment, gastrointestinal membrane permeability, and hypoglycemic effects have been tested *in vitro* and *in vivo*. A variety of pH-responsive carriers are evaluated for their efficacy in delivering insulin effectively into the systemic circulation via the oral route. A range of natural polymers, such as psyllium, starch, pectin, cellulose, and chitosan, are utilized to manufacture oral insulin hydrogels. Hydrogel alters its properties in reaction to variations in pH. In rats with type 1 diabetes, an insulin-containing nano hydrogel demonstrated bioavailability of 6.5% and sustained pH-specific insulin release in the intestine for over 12 hours. The oral administration of insulin-loaded nanoparticles resulted in a significant reduction in blood glucose levels in diabetic rats, which remained very stable for an additional 6 hours. Based on the information provided, it is evident that the nanoparticles loaded with insulin efficiently lower blood sugar levels. The release of insulin from micelles loaded with insulin *in vitro* was pH-dependent. Within two hours, the simulated gastric fluid released less than 20% of the loaded insulin, but the simulated intestinal fluid released more than 60% within ten hours. Microspheres made of cellulose that contain insulin can be released constantly to act as insulin carriers and the release rates of 48% and 85% from artificial stomach and intestinal fluids, respectively, were demonstrated in vitro. Efforts to improve control over size, structure, morphology, and drug loading are necessary to create novel pH-responsive, biodegradable nanostructured materials with high biocompatibility and no toxicity that could be used for oral administration. Additionally, before they may be used, studies must be conducted to determine their biodegradability, distribution mechanisms, and in vivo biotoxicity. Improving current methods and learning more about their biodegradability, dispersion processes, and in vivo toxicity is crucial for developing effective future applications. In order to enhance their therapeutic applications, pH-responsive carriers will be the focus of future research that will thoroughly investigate their physiological environments in vitro and in vivo. Theoretically and pragmatically, exploring the interactions between drug molecules and pH-responsive carriers is crucial for developing new oral drug delivery systems that allow for controlled drug release, increased drug loading capacity, and additional investigation of possible mechanisms. To address these issues with oral insulin administration, researchers are actively developing pH-responsive carriers and investigating a wide variety of other carriers. Hydrogels and nanoparticles, in general, show promise as potential solutions; however, their efficacy will require more study and clinical trials.

Funding: There weren't external funding.

Conflict of Interest: The authors declare no conflict of interest.

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