MS.ID-IJPBS-7781
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2024) 14 (2): 35-42
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Insulin in a Pill: An Overview of Oral Insulin Tablets and Their Potential Impact

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Received: 15 Jan 2024 / Accepted: 6 March 2024/ Published online: 01 April 2024
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Abstract

Diabetes mellitus is one of the fastest-growing global health emergencies of the twenty-first century. Diabetes is a chronic metabolic disease (T2DM) that is characterized by a rapid increase in the incidence of hyperglycemia, hyperlipidemia, and pancreatic -cell destruction. Insulin plays a key role in the regulation of mitosis and cellular functions. It is also a major risk factor for the development of retinopathy, kidney disease, cardiovascular disease, and peripheral vascular diseases. Oral delivery of insulin via the gastrointestinal tract has been shown to be a viable alternative method for treating diabetes. However, there are a few obstacles to overcome, such as the high molecular weight of insulin, the mucin barrier's low diffusion rate, and the protein's vulnerability to enzymatic proteolysis. In addition, multifunctional delivery nano systems have a long way to go before they can be used in clinics, though. The agony of insulin injections may be eliminated for diabetics if insulin delivery nano systems are able to overcome these obstacles.

Keywords

Diabetes, oral insulin, bioavailability, adsorption barriers, oral delivery

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INTRODUCTION:

Ranking among the top ten diseases in the world that pose a threat to human health, diabetes is also one of the fastest-growing global health emergencies of the twenty-first century.

In 1921, JJR Macleod, Charles H Best, and Sir Frederick G. Banting made the initial discovery of insulin at the University of Toronto. James B. Collip then went on to further purify it (1,2). Insulin peptide hormone, which is composed of two peptide chains—the A-chain (21 amino acids) and the B-chain (30 amino acids)—is released by the β-cells of the pancreatic islets of Langerhans. Two disulfide connections join the two chains, while the A-chain has an extra disulfide linkage (3). Insulin makes sure that cells absorb glucose from the blood so that it can be used as fuel. Extra glucose is stored as glycogen. It controls the metabolism of proteins, lipids, and carbohydrates. Insulin promotes mitosis and supports cellular functions (4). When Insulin's ability to act normally is compromised, which leads to hyperglycemia—the main cause of diabetes mellitus and the group of metabolic illnesses. Weight loss, polyphagia, polyuria, and polydipsia are frequently observed symptoms of this illness]. Chronic hyperglycemia is linked to severe symptoms such as retinopathy, kidney, cardiovascular, and peripheral vascular diseases (5,6).

Diabetes mellitus, also known as type 1 or type 2 diabetes, is a chronic metabolic disease (T2DM). Patients with T1DM experience decreased or absent pancreatic insulin production as a result of pancreatic β -cell destruction, while those with T2DM experience low cell sensitivity to insulin (7). As a result, changes in blood glucose homoeostasis are a feature shared by patients with T1DM and T2DM. Hyperglycemia results from elevated blood glucose concentrations caused by low or absent insulin levels (7).

Insulin can be administered most conveniently and safely by oral means, which is also the most accepted mode of administration (11,12). One of its main benefits is that it can prevent problems and hypoglycemia at the site of administration. However, because of its high molecular weight, strong hydrophilicity, poor stability, and low tolerance against protease hydrolysis, oral insulin administration has a bioavailability of less than 2% (13,14,15,16). Furthermore, oral insulin can only function by crossing the gastrointestinal tract's physiological absorption barrier, which has made it more difficult for oral insulin to develop (17,18). However, the oral administration of insulin encounters significant challenges prior to entering systemic circulation. Once insulin travels through the stomach and intestine (9).

By focusing on the lipid bilayers of the epithelial lining of the gastrointestinal tract to overcome the proteolytic enzyme barrier, excipients must be chosen to enhance the stability of absorption and permeability of protein drugs in the gas- trointestinal tract. However, limited studies have been per- formed to study the overall effectiveness of multiple approaches to enhance the bioavailability of orally administered insulin Nevertheless, few research has been conducted to examine the combined efficacy of various strategies for improving the bioavailability of insulin administered orally. Protein and peptide carriers, including liposomes, emulsions, nanoparticles, and microspheres, have been employed to enhance the physical stability of insulin formulations and shield them from digestive enzymes (9,10).

PROCEDURES AND TECHNOLOGIES

How to make tablets of insulin:

The study employed the wet granulation process to prepare coated and uncoated insulin tablets. The active component was powdered human recombinant insulin (Sigma-Aldrich, St Louis, MO, USA). Additional excipients used in the tablet formulation were of standard pharmaceutical grade and included sodium glycocholate (Sigma-Aldrich), meta cresol (Sigma-Aldrich), lactose (Sigma-Aldrich), glycerin (Pharma Scope, Welshpool, WA, Australia), 5% polyvinylpyrrolidone (Thermo Fisher, Malaga, WA, Australia), and Avicel (Sigma-Aldrich).

The formula which displays the quantity and purpose of the selected excipients, was followed in the production of the coated and uncoated insulin tablets. Insulin and the powdered excipients were combined using a mortar and pestle to create a uniform mixture. 5% polyvinylpyrrolidone was then gradually added and triturated. Put well into this mixture. To extract the necessary grains, the wet mass was sieved through a 1016-lm sieve and placed into a metal tray. The resulting wet granules were dried in a stability chamber for fifteen minutes at 40 % humidity and 10 $^{\circ}$ C. After that, the dry grains were sieved using a 711-lm sieve, after which it was put into a magnesium container Prior to compression, stearate and combine for 15 minutes. The granules with a Manesty F3 single-punch compressor tablet press (United Kingdom, Manchester). The blows delivered throughout the process of compression were typically concave and flat just 3.97 mm deep. Setting the eccentric lever to 24 gave Each pill has a 4–6 kg/cm2 average hardness. On average, the tablet that was obtained weighed 94.75 mg. Likewise, coated There were tabletsModes:2 prepared using appropriate quantities of ingredients (Table 1), followed by manual spraying of cellulose acetate hydrogen phthalate solution (Sigma-Aldrich) to form consistent enteric coated layers. Each layer was dried for 2 min before a new layer was sprayed on the tablet manually. The tablets were coated by rolling on the sieve manually throughout the process, and drier was used at the end. Each layer was dried for 2 min before a new layer was coated on the table formed with the proper constituent amounts and then manually sprayed with cellulose acetate hydrogen phthalate solution (Sigma-Aldrich) to create uniform enteric coated layers. Before applying a fresh coat manually to the tablet, each layer was allowed to dry for two minutes. Throughout the process, the tablets were coated by physically rolling them on the sieve, and drier was applied at the conclusion. Before applying a fresh layer on the table, each layer was allowed to dry for two (19).

Formulation 1 (uncoated insulin tablets)				Formulation 2 (coated insulin tablets)	
Ingredients	Function	Manufacturer	Quantity	Ingredients	Function
Insulin	Active ingredient	Sigma-Aldrich, MO, USA	5 mg	Insulin	Active ingredient
Avicel	Disintegrant	Sigma-Aldrich, MO, USA	10 mg	Avicel	Disintegrant
5% Polyvinylpyrrolidone	Binder	Thermo Fisher, Vic., Australia	q.s	5% Polyvinylpyrrolidone	Binder
Magnesium stearate	Lubricant	Thermo Fisher, Vic., Australia	4 mg	Magnesium stearate	Lubricant
Metacresol	Preservative	Sigma-Aldrich, MO, USA	3 mg	Metacresol	Preservative
Lactose	Filler	Sigma-Aldrich, MO, USA	73 mg	Lactose	Filler
Glycerine	Anti-precipitation	PharmaScope, WA, Australia	2 mg	Glycerine	Anti-precipitation
Chitosan	Absorption enhancer	Sigma-Aldrich, MO, USA	2 mg	Chitosan	Absorption enhar
Sodium glycocholate	Enzyme inhibitor	Sigma-Aldrich, MO, USA	1 mg	Sodium deoxycholate	Enzyme inhibitor
				Cellulose acetate hydrogen phthalate solution	Coating

Formulation used in the production of coated and uncoated insulin tablet:

Analysis of the insulin tablet:

The tablets were assessed using a number of common British Pharmacopeia tests, such as weight variation, friability, disintegration, and hardness, to make sure a satisfactory quality was met (20). By choosing twenty tablets at random, the weight variation was examined, and the average weight was determined. The official British Pharmacopeia limit of percentage deviation for all tablets is two tablets maximum.no tablets may be more than 5% off from the mean, and the mean cannot be more than 10% off in (20). Using an Erweka friabilator (Erweka, Heusenstamm, Germany), tablets were also assessed for friability, with a 2 g drum rotation speed. First, the fragment-free tablets were weighed together, and then the dust-free tablets were weighed again together. The tablets must have lost no more than 1% of their original weight and show no signs of obvious cracks in order to meet British Pharmacopeia guidelines. In order to pass the test, all six tablets had to dissolve within 15minutes, according to British Pharmacopeia criteria, which were applied to the disintegration test. In The Monsanto hardness tester (Singhla Scientific, Haryana, India) was used to measure resistance to crushing, and a 4–8 kg limit was established (20).

Evaluation techniques:

1.Weight variation.
2.Friability.
3.Disintegration.
4.Hardness.
5.Weight variation.

Erweka friabilator.

Oral delivery of insulin:

There are a number of benefits to taking insulin orally as opposed to other systemic delivery methods. For instance, there are no needle stick injuries, local pain, discomfort, or irritation, nor is there any risk of skin infections from Staphylococcus aureus and Mycobacterium chelone, which are common with injections (21). According to normal human physiology, the pancreas detects an increase in blood glucose levels following a meal and secretes insulin to keep blood sugar levels within normal ranges. Thus, the primary advantage of oral insulin administration over traditional injection insulin delivery, which can cause the injection site to swell and become sensitive over time, is that the former can be less painful (22). For insulin, hepatic first-pass metabolism is advantageous. While parenteral insulin administration increases the risk of hypoglycemia and an immunological reaction in peripheral tissues, oral insulin can lessen these effects even though it is more easily metabolized by the liver. Reducing insulin exposure in the peripheral system minimizes the risk of weight gain, among other benefits (23).

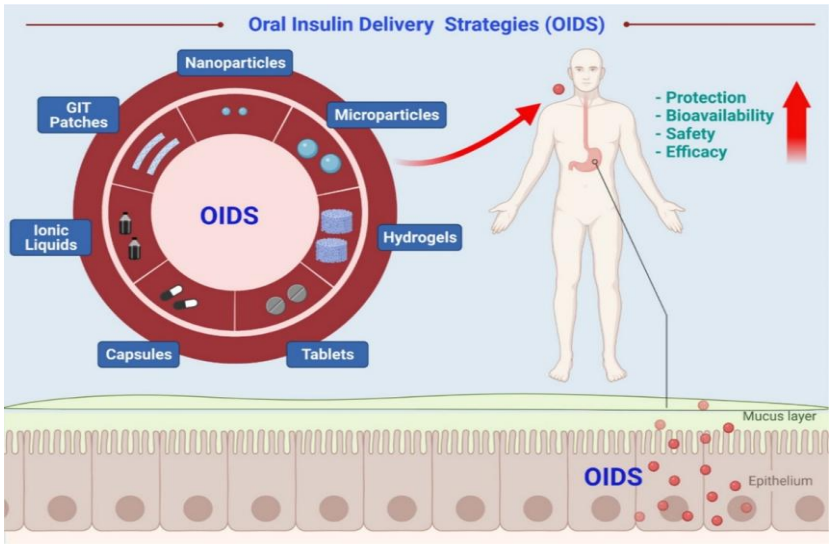
Difficulties in delivering oral insulin through the GIT and potential solutions:

At the moment, less than 1% of oral protein-based medications, including insulin, have oral bioavailability. Therefore, increasing the bioavailability of protein-based medications to 30–50% is the primary goal of their oral delivery (24).

--There are several obstacles to overcome, such as the

1. High molecular weight of insulin
2. The mucin barriers low diffusion rate
3. The protein's vulnerability to enzymatic proteolysis to enzymatic proteolysis.
4. Bioavailability and non-erratic absorption.

--Enzymatic and pH degradation of insulin in the GI: In the stomach and the gastrointestinal tract (GIT), enzyme activity and acidic pH cause insulin to break down quickly. The GIT breaks down insulin due to the action of pepsin and pancreatic proteolytic enzymes like trypsin and α-chymotrypsin (25). Insu-lin is broken down by the stomach's acid catalysis, the intestine's luminal degradation, and the cells themselves. Furthermore, first-pass hepatic insulin extraction causes the liver to break down half of the insulin that gets there. These mechanisms result in low systemic circulation bioavailability of Insulin (26).



Therapeutic activities:

Uncontrolled hyperglycemia can result in a number of negative outcomes for people with T1DM as well as T2DM. It is imperative to maintain long-term blood glucose control in order to minimize the risks associated with both macro and microvascular complications (28). Reducing the incidence of hyperglycemia and the complications it causes is the primary treatment objective for diabetes.

Diabetic ketoacidosis can occur in T1DM patients who purposefully or unintentionally stop taking insulin, particularly the long-acting kind. A significant loss of water and electrolytes from the extracellular and intracellular fluid compartments is a hallmark of diabetic ketoacidosis (29). With respect to patients with T2DM, insulin is normally administered at a later. Stage. At the initial stage or early onset of symptoms, cells in the body cannot utilize or respond to the normal production of insulin effectively. People with T2DM are usually asymptomatic initially, and patients with diabetes may be unaware of their conditions (30).

The first-line treatment currently used is lifestyle modification, which is followed by the therapeutic introduction of metformin (31).When metformin is unable to control blood glucose levels, it is combined with other anti-diabetic medications such as sodium-glucose cotransporter 2 inhibitors, thiazolidinedione, sulphonyl urea's, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 inhibitors, and alpha-glucosidase inhibitors(32,33).In the event that the patient is experiencing ketoacidosis, the initial HbA1c is elevated (≥9.0%), or there is evidence of oral combination medication failure after three to six months, insulin may be necessary in these specific circumstances(33).A specialized multidisciplinary team should manage T2DM patients in order to increase adherence to glycemic control.

Oral insulin	Parenteral insulin
Ease and convenience	Safe and easy route
The pain and chance of skin infection associated with injection is absent	Reduces severe hypoglycemic episodes including nocturnal hypoglycemia
Improves the portal levels of insulin and curtails to the peripheral hyperinsulinemia	Mimics physiological secretion of insulin as closely as technological possible

Minimize the risk of hypoglycemia and immune response	Reduces TDD of limit
An early initiation of insulin therapy improvement in beta cell function with 1year	Slow and sustained absorption. Reduces glycemic variability
Reducing the insulin exposure in the peripheral system, to minimize the incidence of weight gain.	Deliver precise dose of insulin, and basal rate can be adjusted throughout the day

Barriers: -

While oral delivery of insulin is a great substitute administration method for diabetic patients, there are a few obstacles that need to be addressed. Insulin must pass through the stomach and intestine with its complete structure, integrity, and conformation before it can enter systemic circulation. Due to its high molecular weight, low diffusion rate across the mucin barrier, and susceptibility to gastrointestinal enzymes, intact insulin has a low oral bioavailability when administered orally (34). It is a protein medication. Nutrient uptake may occur through paracellular or transcellular processes. In the gastrointestinal tract, simple diffusion and carrier-mediated transport both control transcellular absorption (35). Lipophilic molecules penetrate the epithelial membrane by means of the simple diffusion mechanism. The molecular weight of insulin is 5800 Daltons. The gastrointestinal tract's columnar mucous membrane absorbs it poorly. The membrane structure of the gastrointestinal tract is hydrophobic on the outside and hydrophilic inside (35).

Mucin barrier:

The glycoprotein mucin layer is a crucial barrier that needs to be broken down. The goblet cells' secreted mucus serves to shield the exposed epithelial surfaces by encasing pathogens and foreign particles (36). Unfortunately, the layer's viscous nature makes it function as a physical diffusion barrier, limiting the rate of absorption and bioavailability of oral drug delivery, including protein (36,37).

In this investigation, hyaluronidase was used to remove the mucous layer without compromising the integrity of the cells in the gastrointestinal system (36). When comparing the hyaluronidase-treated segment to the untreated intestinal treatment, the absorption rate and the apparent permeability coefficient (Papp) of insulin are higher (38). Additionally, this study showed that Papp increased in the same order for rats in the hyaluronidase-treated and untreated control groups (ileum < jejunum < duodenum) (38).

Metal Organic Frameworks (MOFs):

A three-dimensional ordered porous material made up of inorganic clusters connected by organic ligands is called a metal organic framework (MOF), also referred to as a porous coordination polymer. Drug delivery makes extensive use of their programmable structures and chemical functions, which are characterized by their regular three-dimensional structure and stable porosity (Figure 2D). Poly (ethylene glycol-b-lactide) is an amphiphilic polymer that can stabilize insulin in the acidic environment of gastric juice. Zhou et al. synthesized iron-based MOFs that could load insulin by physical adsorption (39). The insulin-loaded MOFs could be coated with plastic. Insulin with a molecular size of 1.3 nm × 3.4 nm was able to be loaded into a mesoporous zirconium-based MOF (pore size: 3.2 nm; loading capacity: 40%) that Li et al. pepsin molecules larger than 4 nm were unable to pass through the pores [40). As a result, the loaded insulin was degradable by pepsin. Moreover, this MOF's structural stability in acidic environments prevented the insulin from releasing in gastric juice; in contrast, the MOF's structure could dissolve in PBS, releasing the loaded insulin. These drug delivery materials, however, released their contents too quickly. Under physiological conditions, about 80 percent of the insulin was released in 40 minutes, which could cause adverse effects like hypoglycemia. Currently, medication release must be optimized and regulated gradually. Furthermore, the metabolism pathway and degradation profile are still unknown, which could have detrimental effects on

Premium Label.

Structure of insulin:

Insulin production is a complex process that occurs inside the pancreatic beta cells and is a critical hormone involved in glucose management. Initially, a single chain of the large precursor molecule known as pre-proinsulin is made up of three distinct peptides, A, B, and C. Pre-proinsulin undergoes a series of enzymatic cleavages to yield proinsulin, an intermediate form. By cleaving certain peptide bonds at two separate locations, proinsulin is transformed into mature insulin and the core C-peptide is released. Proteolytic enzymes, notably prohormone convertases PC1, PC2, and mature insulin, aid in this process.

happens by cleaving certain peptide bonds at two different locations, allowing the core C-peptide to be released. The resultant mature insulin is made up of two chains, an A-chain and a B-chain, each of which has 21 and 30 amino acids, respectively, totaling 51

amino acids. Two covalent disulfide connections, CysA7 to CysB7 and CysA20 to CysB19, join these two chains. Furthermore, the A-chain contains an intrachain disulfide bond from CysA6 to CysA11. (41),(42),(43),(44),(45).

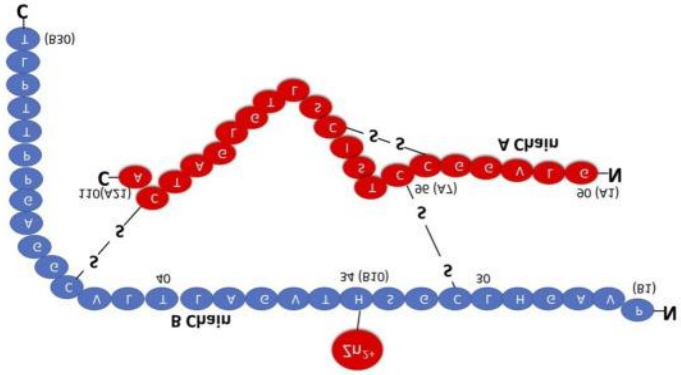


Fig: structure of insulin.

Insulin has a charge of -2 to -6 and an isoelectric point of 5.3 in a pH range of 7–11. When the concentration of insulin in the blood is low, less than 10−3µm, it exists in the bloodstream as a monomer and is physiologically active. However, biosynthesized storage insulin is of crystalline zinc-bound hexamers and is released in response to elevated blood glucose levels in the vesicles of pancreatic β-cells. (46),(47),(48).

Oral insulin delivery:

The oral route is the most advantageous of the well-known insulin administration routes because it most closely resembles the endogenous insulin system. (49)

Following oral administration, the insulin is absorbed from the intestinal lumen and travels via the portal circulation to the liver, where first-pass metabolism commences. After that, the insulin mimics the physiological insulin pathway by entering the peripheral circulation at very modest levels. In contrast, the subcutaneous route is linked to a number of problems, including obesity and peripheral hyper-insulinemia (50),(51)

Nonetheless, the oral delivery of insulin is typically associated with low bioavailability (<2%) for a variety of reasons, including inadequate stability at GI tract pH variations, enzymatic breakdown, and a reduced rate of permeability through intestinal biological membranes (52),(53),(54),(55),(56),(57),(58),(59)

CONCLUSION:

The field of oral insulin delivery has shown great promise in research and could significantly transform the treatment of diabetes mellitus. A number of studies have produced encouraging findings, and some delivery systems are nearing the end of their development. But despite all the efforts undertaken since the 1980s, nothing seems to have changed because the delivery methods that have been developed have not demonstrated a definite clinical advantage over the subcutaneous insulin route. There are several issues that must be appropriately resolved. It is necessary to show long-term safety and efficacy through sufficiently powered studies in various patient populations throughout the diabetes spectrum. Moreover, knowing how the drug is absorbed during meals and achieving a repeatable absorption are crucial objectives for creating a medication that must be taken continuously.

Bioactive Metal-Organic Frameworks (MOFs) are a recent development being investigated for the delivery of insulin orally. Recently, zeolitic-imidazolate framework-8 was used to create a glucose-responsive insulin delivery system of gold nanoparticles (AuNPs) in a single step using a continuous-flow microfluidic mixing system. There may be advantages to administering insulin preparations orally as opposed to through other systemic routes. It can prevent negative effects like weight gain and hypoglycemia. There are several obstacles to overcome, such as the high molecular weight of insulin, the mucin barrier's low diffusion rate, and the protein's vulnerability to enzymatic proteolysis. Bioavailability and non-erratic absorption are the key to the development of oral insulin in the future. An insulin tablet that contains suitable and compatible excipients, such as an enzyme inhibitor, an acid-resistant enteric coating, an absorption enhancer, and a mucoadhesive polymer, may be one way to deliver the medicinal ingredient to the colon, boost insulin bioavailability, and eliminate the small intestine absorption variation that Eigen® and IN-105 encountered. One of the most difficult but potentially effective non-invasive methods for treating diabetes is oral insulin delivery via the gastrointestinal tract. The primary goals of research on oral insulin delivery are to prevent insulin degradation and improve the gastrointestinal tract's ability to absorb it. Additional issues like insulin degradation mediated by

receptors, dosage form stability, and insulin stability in dosage form are also being worked on. Businesses have shown interest in improving patient compliance with oral insulin. Because of the high number of people with diabetes and the drawbacks of insulin injection, research on oral insulin is undoubtedly ongoing. In addition to offering a viable method for delivering insulin orally, the multifunctional delivery nano systems can significantly increase the oral bioavailability of insulin. Oral insulin delivery nano systems have a long way to go before they can be used in clinics, though. More focus on material safety, accurate drug dosage control, preparation process viability, and storage stability should be the focus of future research. The agony of insulin injections may be eliminated for diabetics if insulin delivery nano systems are able to overcome these obstacles.

REFERENCE:

1. D.T. KaramitsosThe story of insulin discoveryDiabetes Res. Clin. Pract. (2011).
2. L.A. DiMeglio et al.Type 1 diabetesLancet(2018).
3. M. Halim et al.The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes)Diabetes Metab. Syndr. Clin. Res. Rev. (2019).
4. O. Kordonouri et al.Treatment of type 1 diabetes in children and adolescents using modern insulin pumps Diabetes Res. Clin. Pract. (2011).
5. J. Wang et al.Mechanism of surface charge triggered intestinal epithelial tight junction opening upon chitosan nanoparticles for insulin oral delivery.
6. S. Ahadian et al.Micro and nanoscale technologies in oral drug delivery.
7. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care 2015; 38(Suppl. 1): 8–16.
8. Bennett, P.H. Diabetes mortality in the USA: Winning the battle but not the war? Lancet 2018,391, 2392–2393.
9. Toorisaka E et al. Hypoglycemic effect of surfactant-coated insulin solubi- lized in a novel solid-in-oil-in-water (S/O/W) emulsion. Int J Pharm 2003; 252: 271–274.
10. Jelvehgari M et al. In vitro and in vivo evaluation of insulin microspheres containing protease inhibitor. Arzneimittelforschung 2011; 61: 14–22.
11. Alvestrand, A.; Wahren, J.; Smith, D.; Defronzo, R.A. Insulin-mediated potassium uptake is normal in uremic and healthy subjects. Am. J. Physiol. 1984, 246, 174–180.
12. Ullrich, A.; Be Ll, J.R.; Chen, E.Y.; Herrera, R.; Petruzzelli, L.M.; Dull, T.J.; Gray, A.; Coussens, L.; Liao, Y.C.; Tsubokawa, M. Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes. Nature 1985, 313, 756–761.
13. Lilong, S.; Zhijia, L.; Houkuan, T.; Zhicheng, L.; Lixin, L.; Leong, K.W.; Hai-Quan, M.; Yongming, C. Scalable Manufacturing of Enteric Encapsulation Systems for Site-Specific Oral Insulin Delivery. Biomacromolecules 2020, 20, 528–538
14. Xu, Y.; Zheng, Y.; Wu, L.; Zhu, X.; Zhang, Z.; Huang, Y. Novel solid lipid nanoparticle with endosomal escape function for oral delivery of insulin. ACS Appl. Mater. Interfaces 2018, 10, 9315–9324
15. Shrestha, N.; Araujo, F.; Shahbazi, M.A.; Makila, E.; Gomes, M.J.; Herranz-Blanco, B.; Lindgren, R.; Granroth, S.; Kukk, E.; Salonen, J. Thiolation and Cell-Penetrating Peptide Surface Functionalization of Porous Silicon Nanoparticles for Oral Delivery of Insulin. Adv. Funct. Mater. 2016, 26, 3405–3416.
16. Ruedy, J. Applied pharmacology. Can. Med. Assoc. J. 1976, 115, 988
17. Xin, H.Z. Overcoming enzymatic and absorption barriers to non-parenterally administered protein and peptide drugs. J. Control. Release 1994, 29, 239–252.
18. Hamman, J.H.; Enslin, G.M.; Kotz, A.F. Oral Delivery of Peptide Drugs. Bio Drugs 2005, 19, 165–177
19. General Medical Council (Great Britain). British Pharmacopoeia. London: Constable, 2013.
20. Finucane K et al. Insulin injection abscesses caused by Mycobacterium chelonae. Diabetes Care 2003; 26: 2483–1484.
21. Khafagy ES et al. Current challenges in non-invasive insulin delivery systems: a comparative review. Adv Drug Deliv Rev 2007; 59: 1521–1546
22. Chen HS et al. Beneficial effects of insulin on glycemic control and β-Cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. Diabetes Care 2008; 31: 1927–1932.
23. Owens DR. New horizons – alternative routes for insulin therapy. Nat. Rev. Drug Discov. 1, 529–540 (2002).
24. Balsubramanian J, Narayanan N, Mohan V, Bindu MS. Nanotechnology based oral delivery of insulin – a retrospect. Int. J. Res. Ayurveda Pharm. 2(4), 144–150 (2013).
25. Park K, Kwon IC, Park K. Oral protein delivery: current status and future prospect. React. Funct. Polym. 71, 280–287 (2011).
26. Fowler MD, Michael J. Microvascular and macrovascular complications of diabetes. Clinical Diabetes 2008; 26: 77–82.
27. Wolfsdorf J et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatr Diabetes 2009; 10: 118–133.
28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl. 1): 62–69.
29. Pawlyk AC et al. Metformin pharmacogenomics: current status and future directions. Diabetes 2014; 63: 2590–2599.
30. Tiwari P. Recent trends in therapeutic approaches for diabetes management: a comprehensive update. J Diabetes Res 2015; 2015: 1–11.
31. Krass I et al. Diabetes management in an Australian primary care population. J Clin Pharm Ther 2011; 36: 664–672.

32. Kempf K et al. ROSSO-in-praxi: a self-monitoring of blood glucose-structured 12-week lifestyle intervention significantly improves glucometabolic control of patients with type 2 diabetes mellitus. Diabetes Technol Ther 2010.12: 547–553.
33. Gardner ML. Gastrointestinal absorption of intact proteins. Annu Rev Nutr 1988; 8: 329–350.
34. Bourdet DL et al. Intestinal absorptive transport of the hydrophilic cation ranitidine: a kinetic modeling approach to elucidate the role of uptake and efflux transporters and paracellular vs. transcellular transport in Caco-2 cells. Pharm Res 2006; 23: 1178–1187.
35. Ensign LM et al. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Adv Drug Deliv Rev 2012; 64: 557–570.
36. Verdugo P. Goblet cells secretion and mucogenesis. Annu Rev Physiol 1990; 52: 157–176.
37. Aoki Y et al. Region-dependent role of the mucous/glycocalyx layers in insulin permeation across rat small intestinal membrane. Pharm Res 2005; 22: 1854–1862.
38. Chen, Y.; Peng, L.; Modica, J.A.; Drout, R.J.; Farha, O.K. Acid-resistant mesoporous metal–organic framework toward oral inslin delivery: Protein encapsulation, protection & release. J. Am.Chem. Soc. 2018, 140, 5678–5681.
39. Cui, Z.; Qin, L.; Guo, S.; Cheng, H.; Zhang, X.; Guan, J.; Mao, S. Design of biotin decorated enterocyte targeting muco-inert nanocomplexes for enhanced oral insulin delivery. Carbohydr. Polym. 2021, 261, 117873.
40. V. Mohan, S.N. Shah, S.R. Joshi, V. Seshiah, B.K. Sahay, S. Banerjee, et al.
41. Current status of management, control, complications and psychosocial aspects of patients with diabetes in India: results from the DiabCare India 2011 Study Indian J Endocrinol Metab, 18 (3) (2014), p. 370 10.4103%2F2230-8210.129715
42. I.B. Hirsch, R. Juneja, J.M. Beals, C.J. Antalis, E.E. Wright Jr.The evolution of insulin and how it informs therapy and treatment choices Endocr Rev, 41 (5) (2020), pp. 733-755,
43. M. Ahmad, L. He, N. Perrimon Regulation of insulin and adipokinetic hormone/glucagon production in flies Wires Dev Biol, 9 (2) (2020), Article e360
44. K. Docherty, D.F. Steiner post-translational proteolysis in polypeptide hormone biosynthesis, Annu Rev Physiol, 44 (1) (1982), pp. 625-638,
45. J.A. Galloway, S.A. Hooper, C.T. Spradlin, D.C. Howey, B.H. Frank, R.R. Bowsher, et al.
46. Biosynthetic human proinsulin: review of chemistry, in vitro and in vivo receptor binding, animal and human pharmacology studies, and clinical trial experience Diabetes Care, 15 (5) (1992), pp. 666-692.
47. D. Allen, C.H. Ruan, B. King, K.H. Ruan Recent advances and near future of insulin production and therapy Future Med Chem, 11 (13) (2019), pp. 1513-1517.
48. Y.W. Chien Human insulin: basic sciences to therapeutic uses Drug Dev Ind Pharm, 22 (8) (1996), pp. 753-789.
49. Z. He, J.L. Santos, H. Tian, H. Huang, Y. Hu, L. Liu, et al. Scalable fabrication of size-controlled chitosan nanoparticles for oral delivery of insulin Biomaterials, 130 (2017), pp. 28-41.
50. S. Seyam, N.A. Nordin, M. Alfatama Recent progress of chitosan and chitosan derivatives-based nanoparticles: pharmaceutical perspectives of oral insulin delivery Pharmaceuticals, 13 (10) (2020), p. 307.
51. A.G. Pittas, N.A. Joseph, A.S. Greenberg Adipocytokines and insulin resistance J Clin Endcor Metab, 89 (2) (2004), pp. 447-452.
52. A. Gedawy, J. Martinez, H. Al-Salami, C.R. Dass, Oral insulin delivery: existing barriers and current counter-strategies J Pharm Pharmacol, 70 (2) (2018), pp. 197-213.
53. F. Benyettou, N. Kaddour, T. Prakasam, G. Das, S.K. Sharma, Thomas Saet al In vivo oral insulin delivery via covalent organic frameworks Chem Sci, 12 (17) (2021), pp. 6037-6047.
54. K. Sonaje, K.J. Lin, S.P. Wey, C.K. Lin, T.H. Yeh, Nguyen HN et al, Biodistribution, pharmacodynamics and pharmacokinetics of insulin analogues in a rat model: oral delivery using pH-responsive nanoparticles vs. subcutaneous injection Biomaterials, 31 (26) (2010), pp. 6849-6858.
55. M.S. Alqahtani, M. Kazi, M.A. Alsenaidy, M.Z. Ahmad Advances in oral drug delivery Front Pharmacol, 12 (2021), Article 618411.
56. C.Y. Wong, H. Al-Salami, C.R. Dass, Recent advancements in oral administration of insulin-loaded liposomal drug delivery systems for diabetes mellitus Int J Pharm, 549 (1–2) (2018), pp. 201-217.
57. W. Shan, X. Zhu, M. Liu, L. Li, J. Zhong, W. Sun, et al. Overcoming the diffusion barrier of mucus and absorption barrier of epithelium by self-assembled nanoparticles for oral delivery of insulin. ACS Nano, 9 (3) (2015), pp. 2345-2356.
58. R.M. Ramesan, C.P. Sharma, Challenges and advances in nanoparticle-based oral insulin delivery Expet Rev Med Dev, 6 (6) (2009), pp. 665-676.
59. T.A. Aguirre, D. Teijeiro-Osorio, M. Rosa, I.S. Coulter, M.J. Alonso, D.J. Brayden, Current status of selected oral peptide technologies in advanced preclinical development and in clinical trials Adv Drug Deliv Rev, 106 (2016), pp. 223-241.
60. D. Sgorla, A. Lechanteur, A. Almeida, F. Sousa, E. Melo, Bunhak É, et al. Development and characterization of lipid-polymeric nanoparticles for oral insulin delivery Expet Opin Drug Deliv, 15 (3) (2018), pp. 213-222.