International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

Oral Insulin Tablets Design

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Date of Submission: 25-07-2024 Date of Acceptance: 05-08-2024

ABSTRACT:
Diabetes mellitus, an endocrine disorder characterized by glucose metabolism abnormalities due to insulin insufficiency, is a significant global health issue. Current treatments often involve insulin injections, which have drawbacks such as patient discomfort and risk of hypoglycemia. Oral insulin delivery presents a promising alternative due to its potential to improve patient compliance and reduce complications.
This review explores the design and development of oral insulin tablets, focusing on overcoming physiological barriers such as enzymatic degradation and poor intestinal absorption. Strategies discussed include the use of nanoparticles for encapsulation, enzyme inhibitors, and absorption enhancers to protect insulin and facilitate its transport across the gastrointestinal tract. Nanoparticle systems, particularly polymer-lipid hybrids, show potential in enhancing insulin stability and bioavailability.
Despite challenges, advancements in oral insulin delivery methods highlight its potential to mimic natural insulin secretion more closely, offering significant benefits for diabetes management by reducing peripheral hyperinsulinemia and associated complications. Further research and development are needed to achieve clinically and economically viable oral insulin products.
Keywords: Diabetes mellitus, Glucose metabolism, Insulin insufficiency, Insulin injections, Hypoglycaemia,Oral insulin delivery, Enzymatic degradation, Intestinal absorption, Nanoparticles, Encapsulation , Enzyme inhibitors , Absorption enhancers , Polymer-lipid hybrids, Insulin stability, Bioavailability, Natural insulin secretion, Peripheral hyperinsulinemia ,Diabetes management.

I. INTRODUCTION:

Diabetes mellitus is an endocrine condition characterised by glucose metabolism abnormalities caused by insulin insufficiency.Diabetes symptoms often include polyuria, polydipsia, polyphagia, and weight loss. The epidemiological study found that hyperglycemia is the leading cause of diabetes. Chronic hyperglycemia causes long-term diabetic complications such as retinopathy, nephropathy, neuropathy, cardiovascular and peripheral vascular problems.According to the World Health Organisation, the worldwide diabetes burden is expected to increase from 118 million in 1995 to 220 and 300 million by 2010 and 2025, respectively. Diabetes is a prominent cause of death and morbidity globally[(1)].

Oral insulin is a promising treatment option for diabetes due to its convenience, ability to quickly deliver insulin to the liver, avoid peripheral hyperinsulinemia, and prevent weight gain and hypoglycemia. Early beginning of intense insulin therapy leads to tighter glycemic control and reduced complications, making effective oral insulin products crucial for diabetes care. Despite being aware of this unmet medical need, oral insulin administration has proven to be ineffective due to a variety of hurdles. For decades, researchers have attempted to develop oral insulin using numerous methods with limited clinical and economic success[(2)].

Diabetes is classified into four kinds, which are as follows:
1.Type I diabetes:The illness often appears in childhood and has a rapid onset, with an average peak age of 12 years old. Exogenous insulin is required for patients' survival. Type I diabetes affects 10% of adults over the age of 65[(1)].
2. Type II diabetes: The condition often develops gradually and later in life. Patients may or may not need exogenous insulin. Type II diabetes results from both polygenic and monogenic disorders. Genetic factors can increase the risk of developing diabetes.The condition is more severe in Type II diabetic individuals than to Type I[(1)].
3. Gestational diabetes: Diabetes symptoms often emerge during pregnancy[(1)].
4. Genetic problems of beta cells, type A insulin resistance and/or receptor mutation, medicines, chemicals, or illnesses that cause pancreatic

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

damage, endocrinopathy, and other factors may also cause certain forms of diabetes[1].

Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) cause a gradual decline in β-cell activity. In T1DM, autoimmune destruction causes rapid loss of β-cell function. In early T2DM, the disease is characterised by reduced first-phase insulin release, lack of prandial suppression of hepatic glucose production, increased postprandial glucose (PPG) excursions, and late insulin hypersecretion. Late stage T2DM causes considerable loss of pancreatic β-cell mass, resulting in low endogenous insulin output[2].

Therapy for T1DM or T2DM aims to: (i) eliminate hyperglycemic symptoms, (ii) minimise long-term microvascular and macrovascular consequences, and (iii) enable patients to maintain a normal lifestyle. Several ways may be needed to attain these aims. T1DM therapy begins with insulin, whereas T2DM care involves medical nutrition therapy, lifestyle changes, and metformin. If metformin alone does not offer glycemic control, a combination treatment with OHAs or basal insulin is recommended. To manage PPG fluctuations when endogenous insulin production decreases, short-acting and long-acting insulin injections are administered many times[2].

THE EVOLUTION OF INSULINS:

Insulin has changed over the course of a century of usage, and a wide range of choices are now accessible by altering either its structure or formulation. It was exclusively taken from animal pancreas in the beginning, and its profile was ill-defined and irregular. Nowadays, the primary methods for simulating endogenous insulin secretion are recombinant human insulin and insulin analogs with established pharmacokinetic (PK) and pharmacodynamic (PD) characteristics[3].

Currently available insulins and their action time are described below,

Type of insulin		**Onset time**	**Peak time**	**Duration of action**
Ultrarapid-acting				
	Insulin aspart (Fiasp®)	4 min	1–3 hr	3–5 hr
	Insulin lispro-aabc (Lyumjev®)	2 min	1–2 hr	~4.6 hr
Rapid-acting				
	Insulin lispro (Humalog®)	10–15 min	1–2 hr	3–5 hr
	Insulin aspart (NovoRapid®)	10–15 min	1–3 hr	3–5 hr
	Insulin glulisine (Apidra®)	10–15min	1–2 hr	2–4 hr
Short-acting				
	Regular insulin (Humulin R®)	30 min	2–3 hr	6.5 hr
Intermediate-acting				
	NPH insulin (Humulin N®)	1–3 hr	5–8 hr	~18 hr
Long-acting				
	Insulin glargine (Lantus®)	1.5 hr	No peak	~24 hr
	Insulin glargine U300 (Toujeo®)	~6 hr	No peak	24–36 hr
	Insulin detemir (Levemir®)	3–4 hr	6–8 hr	~24 hr
	Insulin degludec (Tresiba®)	30–90 min	No peak	~42 hr
Premixed				

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Type of insulin		Onset time	Peak time	Duration of action
	70% NPH+30% regular insulin (Humulin® 70/30)	30–60 min	Dual (NPH & regular)	10–16 hours
	25% lispro+75% neutral protamine lispro (Humalog® Mix25)	5–15 minutes	Dual (lispro protamine & lispro)	10–16 hours
	50% lispro+50% neutral protamine lispro (Humalog® Mix50)	30-60min	Dual (lispro protamine & lispro)	10–16 hours
	30% aspart+70% neutral protamine aspart (Novomix® 30)	5–15 min	Dual (aspart protamine &aspart)	10–16 hours
	50% aspart+50% neutral protamine aspart (Novomix® 50)	30–60 min	Dual (aspart protamine &aspart)	10–16 hours
	70% degludec+30% aspart (Ryzodeg®)	15 min	Dual (degludec&aspart)	> 40 hours

NPH, Neutral Protamine Hagedorn [4].

The original soluble insulin formulation had a short half-life, necessitating large volume injections several times a day, and a significant risk of hypoglycemia. When Hans C. Hagedorn discovered that adding protamine might extend the impact of insulin, he created the first insulin formulation with prolonged action in 1936. Prior research utilizing insulin emulsions in oil and lecithin or in conjunction with vasoconstrictors did not provide reliable outcomes. Since insulin's isoelectric point was below physiological pH (about 5.2), Hagedorn used the idea that proteins are least soluble at isoelectric pH and selected the very basic protein protamine. With insulin hexamers, protamine crystallizes and dissolves gradually upon injection.As a result, there is a delay in the release of insulin hexamers and the circulation's absorption of monomers. In 1946, Nordisk created isophane insulin, also known as neutral protamine Hagedorn (NPH) insulin, by combining protamine insulin with zinc. By acting for a longer period of time and being able to be combined with conventional insulin in the same syringe, NPH enhanced patient acceptance and glycemic control when administered twice daily. Developed in the early 1950s, lente and ultralente insulin had a longer duration than NPH; nevertheless, because of considerable daily variability in absorption, irregular peak patterns, and incompatibility with normal insulin, its usage was restricted. The development of anti-insulin antibodies, which causes insulin resistance and lipoatrophy, is a typical disadvantage of animal insulins. Thus, until the early 1980s, techniques for producing highly pure preparations were crucial[4].

Recombinant deoxyribonucleic acid (DNA) technology was used to create insulin, the first therapeutic protein that the U.S. Food and Drug Administration (FDA) licensed for use in humans in 1982. Genes were successfully expressed in 1978 and 1979 using this technique, which was developed in the 1970s and involved cloning and expressing genes in Escherichia coli. The A and B chains of insulin's genes were created using the amino acid sequence at the time as the human insulin gene sequence was unknown. The first human insulin, Humulin, is still in widespread use thanks to the cooperation of scientists working on chemical DNA synthesis, bacterial and mammalian gene regulation, restriction enzyme-based recombinant DNA technology, cloning

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vectors, and industry support (Genentech, San Francisco, CA, USA; and Eli Lilly).

Aspart and glulisine, two fast-acting insulins with comparable profiles that were created and released later, are currently thought to be superior lunchtime insulins due to their comparable effectiveness and decreased risk of hypoglycemia when compared to conventional insulin. Oftentimes, basal insulin is the first line of therapy for diabetes because it helps keep blood sugar levels stable during the night and in between meals.

Before insulin glargine was authorized in 2000, NPH insulin served as basal insulin for around 50 years. To flatten the peak and provide a longer acting profile, two arginines were added at locations B31 and B32 and glycine was substituted for asparagine at position A21. The isoelectric point was changed to almost neutral pH by these changes in amino acid sequences, which improved chemical stability in a low pH solution. Thus, insulin glargine injection causes precipitation triggered by pH and delayed release, allowing for steady activity.

More recently produced long-acting analogs, such as insulin glargine U-300 (3-fold concentrated) and insulin degludec, were authorized in 2015. In insulin degludec, lysine at position B29 receives a side chain of 16-carbon fatty acid via a glutamic acid spacer, and the threonine at position B30 is eliminated. Insulin degludec is now the longest-acting insulin analog, with a duration of action of 42 hours, due to the formation of mutihexamer complexes upon subcutaneous injection that greatly delay dissociation and absorption. Compared to first-generation long-acting analogs, these more recent analogs provide a decreased risk of hypoglycemia, a more physiological basal profile, and comparable effectiveness.

There are also a number of premixed insulins that offer convenience, the ability to avoid mixing mistakes, and the need for fewer shots. These are more suited for people who lead normal lives, nevertheless, as the ratio of each component cannot be easily changed. Currently available are human insulin mixes (NPH insulin with ordinary insulin), analog insulin mixtures (rapidacting insulin analogs plus its protonated solution), and a combination of aspart and insulin degludec[4].

Role of oral insulin:

Since the discovery of insulin by Banting and Best in 1922, several researchers have worked toward the objective of administering insulin orally. On the other hand, insulin's oralbioavailability is often less than 10%. According to reports, less than 0.5% of insulin taken orally makes its way into the bloodstream.Normally, proteins cannot pass through the intestinal epithelium undamaged. Rather, before to absorption, they will be disassembled into their component free amino acids. The medicine insulin has a molecular weight that is quite high and is hydrophilic. Insulin does not go through intestinal cells via a particular transport mechanism[1].

Hepatically administered oral insulin can provide high insulin concentrations in the portal vein without causing prolonged peripheral hyperinsulinemia. The physiological justification for oral insulin has been widely examined. In the early stages of type 2 diabetes, the body's ability to produce insulin in response to a meal is impaired. Somatostatin infusion in normal individuals proved the significance of suppressing early insulin production, highlighting its physiological value. Researchers found that non-oxidative glucose elimination led to higher glycemic excursions and decreased energy expenditure. Research suggests that replacing the early surge in insulin in type 2 diabetes patients can significantly lower glycemic excursions.

A fast-acting oral insulin that replicates the early insulin response to meals and restores the portal-to-peripheral gradient is greatly desired. Oral insulin may benefit T2DM patients by promoting β-cell rest, slowing disease progression, reducing insulin exposure to peripheral tissues, and preventing late postprandial hyperinsulinemia (if short-acting).

Chen et al. found evidence that early insulin introduction can reverse decreased β-cell activity in newly diagnosed severely hyperglycemic T2DM patients, compared to oral antidiabetic medications. In the sixth month of the trial, the homeostasis model assessed β-cell function index and insulin area under the curve, in addition to lowering HbA1C levels[2].

General Methods for Developing Oral Insulin:

Insulin delivery by oral route is problematic due to physiological constraints. The digestive tract secretes enzymes such as pepsin, which acts as an early barrier.The enzymes trypsin, chymotrypsin, carboxypeptidase, and pancreatin break down big proteins into smaller peptides and amino acids. Proteins in the digestive tract are quickly broken down and only a small percentage are absorbed intact.

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

Insulin that remains intact in the digestive tract must be absorbed systemically. The gastrointestinal tract (GIT) walls consist of a single layer of firmly linked columnar cells, creating a barrier to absorption. Occludins are hydrophobic proteins that closely bind cells together. Mucin, a heavily glycated protein, serves as a gel filtration membrane, preventing bigger molecules from being absorbed. The epithelium layer contains non-specific digesting protease enzymes capable of degrading proteins[(2)].

Insulin administration by oral route:

Compared to alternative systemic administration routes, oral insulin delivery has various advantages. Injections do cause local pain, discomfort, irritation, needlestick injuries, or the risk of skin infections from Staphylococcus aureus and Mycobacterium chelonae. The pancreas detects an increase in blood glucose after a meal and secretes insulin to maintain normal levels. Oral insulin has the advantage of being less unpleasant than injection insulin, which can cause sensitivity and inflammation in the injection site over time.

Oral insulin treatment enhances drug levels in the portal and reduces peripheral hyperinsulinemia, which can cause neuropathy and retinopathy when administered through other methods. Hepatic first-pass metabolism is advantageous to insulin. Although oral insulin is less bioavailable due to hepatic metabolism, it reduces the risk of hypoglycemia and immunological response in peripheral tissues compared to parenteral delivery. Additionally, lowering insulin exposure in the peripheral system can help prevent weight gain.

Early beginning of 6-month insulin therapy, particularly in T2DM patients with severe hyperglycaemia, leads to improved b-cell activity within a year. The oral form of insulin administration is convenient and reduces side effects including weight gain and hypoglycemia. This can lead to early commencement and compliance with insulin therapy, reducing the course of diabetes[(5)].

Barriers to Oral Protein Delivery:

Oral insulin delivery is a promising option for diabetic patients, but there are certain challenges to overcome. Insulin must pass through the stomach and intestine without losing its shape, integrity, or conformation before entering the bloodstream. Insulin's limited oral bioavailability is due to its large molecular weight, vulnerability to gastrointestinal enzymes, and slow absorption over the mucin barrier[(5)].

STRATEGIES FOR ORAL INSULIN DELIVERY:

In light of the challenges associated with oral insulin administration, many approaches have been devised. An effective oral delivery method should prevent considerable toxicity, enhance intestinal penetration, provide delayed or regulated release, shield insulin from acidic pH and enzyme action in the GIT, and achieve direct administration to a particular cell or tissue.

1. Encapsulation into Nanoparticles

Insulin has been administered orally using a variety of nanoparticle forms. The most popular types are polymeric and inorganic nanoparticles, where the medication is enclosed in a biocompatible and biodegradable polymeric matrix, such as dextran or polylactic-co-glycolic acid (PLGA), enabling oral bioavailability and targeted target delivery. Solid Lipid Nanoparticles (SLNs), which are lipid-based nanoparticles, are made of systems that are stabilized with surfactants to keep them in a solid form at room temperature and in the body. They are not greatly impacted by acidic pH or proteases. However, their ability to trap insulin inside their matrix is limited due to their hydrophobic surface.

The combination of lipids and polymeric components, known as hybrid systems, increases the drug's permeability across the epithelial membrane by increasing lipophilicity and the polymers' mucoadhesion. These components also demonstrate resistance to enzymatic degradation. This demonstrates the benefits of hybrid systems by allowing the insulin to be protected until it reaches the gut pH, which raises the drug's passive diffusion.

Particularly in liposomelike structures or solid lipid particles, the organization and stability of hybrid systems are guaranteed by the hydrophilic core containing insulin and the hydrophobic character of the lipids. Since these systems are made of biocompatible materials and have the right dimensions for insulin to pass through the membrane, they are also regarded as innovations for the transport of insulin through the oral route, which looks very promising and is dedicated to revolutionizing the treatment of diabetes. The polymer-lipid hybrid systems that load insulin are made up of a restricted number of polymers and a wide variety of lipids. Testing a variety of synthetic and natural polymers—

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

including chitosan, lecithin, and PLGA—showed that every formulation exhibited mucoadhesive qualities, enhanced the lipophilicity of transporters, and was biocompatible.

Insulin can be better absorbed via the gastrointestinal tract (GIT) by using mucoadhesive polymers, which stick to the mucosa of the gastrointestinal tract and prevent insulin from degrading. Additionally, these mucoadhesive polymers can be employed as encapsulating agents to transfer insulin into nanoparticle systems like alginate and chitosan. Because of its nontoxic, biocompatible, and biodegradable properties, chitosan is one of the best polymers to utilize. It can also shield insulin from deterioration and perhaps increase its absorption by interacting with the occlusive junctions that separate epithelial cells. Another popular polymer for delivering proteins and peptides with mucoadhesive qualities orally is alginate. In addition, it is pH-sensitive, biocompatible, and biodegradable. Another popular polymer for delivering proteins and peptides with mucoadhesive qualities orally is alginate. In addition, it is pH-sensitive, biocompatible, and biodegradable. In order to increase alginate nanoparticle durability in an acidic pH, chitosan coating is frequently used. This enhances protein delivery by oral administration and achieves tailored release in the gut.

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2. Enzyme Inhibitors and Absorption Enhancers

It is possible to enhance oral insulin administration using techniques other than the use of nanoparticles. The most often used approach among them is the use of enzyme inhibitors, which can get beyond the proteolytic barrier of the oral insulin route.

An illustration of this approach's application can be found in a study that used an enzyme inhibitor made from avian egg white. The researchers' findings suggested that using this kind of compound would effectively shield insulin from trypsin and alpha-chymotrypsin for up to an hour. However, a large quantity of enzyme inhibitors must be given in order to accomplish insulin absorption, which may change the gastrointestinal enzymes and cause food proteins and peptides to be poorly absorbed.

Utilizing absorption enhancers is an additional strategy that may improve transcellular and paracellular absorption by altering the structure of the lipid bilayer. Reversible, safe, non-toxic, non-irritating, and non-allergic profiles are ideal for absorption enhancers. They should also have no pharmacological effects and be permitted to quickly improve permeability—ideally while the medication is in the absorption site. These include chelating compounds, chitosan, bile salts, fatty acids (laureates, caprylates, and palmitic acid), surfactants like Labrasol, and bile salts. It has also been demonstrated that these agents improve permeability. Patients who are obese have elevated amounts of palmitic acid, a saturated fat that is produced when triglycerides in the diet break down. Because it activates toll-like receptors in cell membranes, palmitic acid triggers inflammation. Once within the cell, it transforms into ceramides, diacylglycerol, and phospholipids. These products function as proinflammatory mediators, which trigger the activation of reactive oxygen species and protein kinases C. In contrast to palmitate alone, Bunn et al. previously demonstrated that insulin combined with palmitic acid induced the synthesis of interleukin-6 and tumour necrosis factor-α in human monocytes.

Long-term usage of absorption enhancers can harm the biological barrier, making it easier for toxins and pathogens from the gut flora to enter the circulation and cause localized inflammation and infections—despite the obvious benefits. Additionally, some of them—such as bile salts and surfactants—are hazardous; for this reason, short-term usage is advised [(7)].

3. Cell Permeation Peptides

Since they permit the internalization of many molecules into cells, it has been demonstrated that the combination of therapeutic proteins and cell penetration peptides would be a viable strategy for the administration of macromolecules. The short peptide sequences that make up the cell penetration peptides are rich in basic residues like arginine and lysine, which inhibit electrostatic interaction with negatively charged molecules on the cell surface. They also have a non-specific delivery approach. It has been demonstrated that insulin's intestinal bioavailability is increased when it is conjugated to these substances. Despite their innocuous effects, they may slightly disrupt the membranes, which

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

increases the amount of peptides and proteins absorbed orally.

Furthermore, extracellular and intracellular enzymes have the ability to break down the chemical instability of the cell penetration peptides. As a result, several tactics have been created to increase their safety and stability. According to Nielsen et al., insulin absorption may be boosted by cell-penetrating peptides like penetratin, an amphipathic and cationic molecule. They found that D-penetratin raised insulin bioavailability to 18.2% and that when D-penetratin was given, the half-life of insulin rose from 24.9 ± 4.5 min to 90.5 ± 11.8 min.

Insulin permeability may potentially be impacted by intermolecular interactions between the cell-penetrating peptide and insulin. Kamei et al. demonstrated that only gastrin, glucagon-like peptide-1, bonded to octoarginine D-R8, a peptide that is well known to penetrate cells, out of 16 different peptides. As such, the presence of D-R8 enhanced the absorption of insulin, while peptides lacking an affinity for D-R8 were not absorbed [(8)].

4. Intestinal Patches

Typically, these systems consist of circular discs made of polymers (such as carbopol and carboxymethylcellulose) that shield the medication from the GI tract while allowing it to be absorbed. This results in the medication building up at the site of action and releasing it in a regulated and unidirectional manner. The ability of these patches to promote the peristaltic motions of the intestine and the passage of food and fluids is indicated by studies that demonstrate their mucoadhesion to the gut. The patches might be coated to survive the stomach's acidic pH and stop the release of insulin. Although permeability enhancers were absent from the first generation of patches, they appeared to promote insulin absorption.

The most often used permeation enhancers in the patches were hydrogenated oils, surfactants (such sodium lauryl sulfate and Labrasol), and surfactants.For the purpose of delivering insulin orally, Gupta et al. created ethyl cellulose patches that included 0.5% w/v of the permeability enhancer dimethyl palmitoyl ammonia propane sulfonate. In Caco-2 monolayer cells, they saw a considerable rise in insulin and exenatide flow. In a recent study, Banerjee A. et al. created micropatches with a proteases inhibitor and a permeation enhancer that stuck to the intestinal mucosa and released insulin in 30 minutes, resulting in a 34% decrease in blood glucose levels[(9)].

5. Insulin Conjugation

A further strategy to improve insulin's bioavailability is to employ the cell's own endocytic route to absorb macromolecules necessary for cell survival. Receptors that identify certain chemicals that enter cells through transcytoses mediate this process. Transcellular delivery may be possible when these molecules are combined with therapeutic peptides. The protein transferrin is involved in the transcellular transport of iron and is a commonly utilized ligand to improve medication absorption, including therapeutic genes, peptides, and anti-tumour medicines. Using a radioimmunoassay, Xia et al. created transferrin-insulin conjugates and evaluated their stability in relation to free insulin in rat liver slices. In diabetic rats, the in vivo studies demonstrated a dose-dependent extended hypoglycemic effect in comparison to free insulin. Additionally, blood serum was found to contain insulin-transferrin conjugates, indicating that the conjugates cross intact endothelial cells.

In streptozotocin-induced diabetic rats, Xia and Shen examined the transport of the insulin-transferrin conjugate in Caco-2 cells. When tyrphostin-8 is present, there is an increase in the transport of insulin-transferrin. Moreover, in comparison to the other permeation enhancers examined, tyrphostin-8 exhibited lower cytotoxicity. At seven hours after injection, the presence of tyrphostin-8 caused the greatest hypoglycemic impact. Free insulin and insulin conjugated with serum albumin, on the other hand, did not exhibit any hypoglycemic effects. Kavimandan et al. demonstrated that the hydrogel-based delivery system for insulin-transferrin conjugates protected insulin against enzymatic degradation by electrospray ionization mass spectrometry, in addition to the evidence that the disulfide bonds used to bind ligand transferrin and insulin have been suggested to improve the oral bioavailability of insulin in diabetic rats[(9)].

Improving Insulin Delivery Through Oral Routes:

Insulin's hydrophilic nature and large molecular size result in low oral bioavailability and gastrointestinal permeability. Technological advancements enabled peptide formulations, such as calcitonin, to circumvent these limitations. Calcitonin, a polypeptide hormone released by the

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

thyroid gland, lowers blood calcium levels, inhibits bone resorption, and increases urine calcium excretion[10].

It uses parenteral or intranasal delivery to treat postmenopausal osteoporosis, Paget's disease of bone, and hypercalcaemia[11][12].

Calcitonin has been successfully manufactured and tested in phase 3 utilising an acid-resistant enteric coating that resists dissolving in the stomach. Citric acid added to the tablet core inhibits intestinal proteases and improves paracellular transport[13].

Using this strategy may improve oral communication skills.Numerous protease inhibitors have been studied, including camostatmesilate, soybean trypsin inhibitor, bacitracin, sodium glycocholateandaprotininto evaluate its efficacy in preserving insulin stability. However, using enzyme inhibitors may result in adverse consequences such pancreatic enlargement and hyperplasia, as well as systemic intoxication. It has been discovered that the long-term use of soybean trypsin inhibitors causes invasive cancer[14][15].Enzyme inhibitors, absorption enhancers (bile salts, lysolecithin, sodium dodecyl sulphate are used) mucoadhesive polymers (chitosan and PLGA), and chemical modification are effective ways for improving the bioavailability of oral insulin[2].

Endogenous receptor-mediated absorption. Oral colon-specific insulin administration using protease inhibitors, permeability enhancers, and polymers has been studied to improve therapeutic drug bioavailability. Three types of delivery methods exist: pH-dependent, time-dependent, and microflora triggered. Colon targeted administration has several benefits, including longer retention duration near the epithelial surface, lower expression of P-glycoprotein, increased responsiveness to permeation enhancers, and lower concentration of proteolytic enzymes. Developing an oral insulin formulation for the colon might improve absorption and bioavailability in the small intestine, avoiding unpredictable results[5].

Tabletting of Insulin:

Oral insulin in solid dose form provides a more convenient alternative to injections for diabetes therapy. Oral delivery is a preferred method of administration due to its non-invasiveness. This evaluation focuses on difficulties related to oral insulin tablets[5].

Oral Insulin Tablet Products:

Currently, two oral insulin tablet products are in clinical studies. Emisphere Technologies filed a patent application in 2007 for insulin delivery formulations[16]. Tablet manufacture relies heavily on granulation, which can be dry or wet. During the granulation step, tiny fine drug particles and excipients are spread uniformly. Agglomeration is the process that converts powder particles into granules[17].Emisphere Technologies used both dry granulation (roller compaction) and wet granulation (granulation liquid/binder) for tablet manufacture.

This business employed povidone and dibasic calcium phosphate (binder) in the wet granulation process to enhance agglomeration and the formation of a wet material for tabletting[5].

Eligen: Emisphere Technologies (USA):

The initial oral tablet formulations included insulin plus a drug carrier, monosodium N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB), which binds non-covalently to insulin and enhances gastrointestinal absorption through a reversible combination. This compound alters insulin's physiochemical characteristics and may easily pass through the gastrointestinal epithelial membrane via diffusion. After absorption, oral insulin dissociates from 4-CNAB and enters the liver at a high concentration via the portal vein. This results in a more physiological hepatic response and a larger influence on liver glucose production. Emisphere's technology protects peptides ranging from 500 to 1500 Da from digestion and improves absorption. Research included eight male patients with T2DM (BMI <32 kg/m2), both with and without a meal. When taken 10 minutes before a meal, a combination of 300 units of insulin and 160 mg 4-CNAB tablet formulation resulted in a larger drop in blood glucose levels compared to other ratios and delivery times. The prandial stage has a lower mean maximum concentration (Cmax = 65 lU/ml vs 17065 lU/ml) and a shorter time to reach Cmax (tmax = 15 min vs 20 min).A parallel-group trial with thirteen male and female patients (BMI <32 kg/m2) evaluated the efficacy of an oral pill over two weeks. The study found a decrease in fasting blood glucose levels, better insulin secretion, and no adverse effects such as systemic hyperinsulinemia, hypoglycemia, or weight gain. However, this study found significant variance in oral insulin absorption and limited clinical utility. Regional variations in absorption and distribution of proteolytic enzymes may contribute to the issue mentioned above. More comprehensive and longer-term trials with a large sample of non-fasting T1DM patients are needed to explore the blood glucose-lowering impact of insulin[5].

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IN-105: Nobex and Biocon (India):

This oral delivery method uses Nobex technology. Nobex technology modifies recombinant human insulin using PEG and penetration enhancers. Biocon developed IN-105, a modified insulin analogue, and administered it orally via tablets. IN105 gained hydrophobicity by linking lysine residues in insulin's beta chain with an amphiphilic oligomer. This chemical alteration improved solubility by PEGylating, gastrointestinal absorption, and insulin stability through steric inhibition. IN-105 is a fast-acting oral insulin analogue[(18)].The beginning of action is comparable to Eligen, which can regulate postprandial glucose levels within 30 minutes.This insulin analogue was tested on 20 T2DM patients (BMI <29 kg/m2) who had poor blood sugar control with extended-release 500-1500 mg metformin medication for 12 weeks prior to the trial. Four dosages (10 mg, 15 mg, 20 mg, and 30 mg) were given 20 minutes before a meal in five consecutive times. The study found that increasing the dose of the drug resulted in increased absorption and reduced 140-minute postprandial glucose levels. Blood glucose levels were reduced by 18%, 26.1%, 29.0%, and 30.8%, respectively. Cmax values varied dramatically across four dosages (50 mU/l to 350 mU/l). However, all dosages had the same tmax (30 minutes). This phase 3 trial found several negative effects in T2DM patients. Five individuals suffered hypoglycemia (blood glucose levels < 70 mg/dl) within 30-60 minutes after receiving IN-105 (15-30 mg doses). In one case, the patient reported hypoglycemic symptoms while having blood glucose levels above 150 mg/dL. The study suggests that hypoglycemia occurs when blood sugar levels drop rapidly from 250 to 150 mg/dl. Adverse effects included elevated serum triglyceride levels, disorientation, and hyperhidrosis. Although greater dosages were found to improve absorption and postprandial glucose management in the study, undesirable effects must be considered when establishing the optimal dosage[(5)].

Intesulin: Coremed

The process of encapsulating insulin in bio adhesive polymer nanoparticles yields Intesulin, a long-acting insulin. Research done on diabetic rats given streptozotocin shown a statistically significant drop in blood glucose levels starting 15 minutes after delivery and continuing for 300 minutes. There are currently no human data accessible in the literature[(2)].

Oramed:

An oral insulin capsule created by Oramed (Jerusalem, Israel) has been tested in preliminary clinical studies. The insulin is released in the colon via an enteric coated capsule; the use of a PE facilitates absorption. In order to determine the best formulation, a study involving eight healthy volunteers showed that giving an oral form of insulin while fasting reduced blood glucose levels (7–37%) and significantly decreased C-peptide levels (13–87%) in all formulations. The volunteers all responded well to all of the formulations, and no significant side effects have been documented.

This insulin took more than two hours to start working and took up to five hours after injection. Lack of control over the timing of insulin release is one of the possible problems associated with delayed insulin release. Food impacts and GIT motility may have a negative impact on the release of insulin as it occurs in the gut. To fully comprehend the technology's long-term impacts and genuine glucose-lowering potential, further data on diabetic patients who are eating will be needed [(2)].

Hepatic-directed vesicles-insulin (HDV-I): Diasome Pharmaceuticals

Hepatic-directed vesicles-insulin (HDV-I) in subcutaneous administration is the liposomal insulin medication delivery technology that Diasome Pharmaceuticals is creating as well as versions taken orally. The results showed statistically significant reductions in mean and incremental PPG area-under-curve as measured over a period of 14 h (30 min before breakfast dosing to 4.5 h after dinner) as compared to placebo in a placebo controlled, dose-ranging trial of oral HDV-I in six patients with T2DM; however, dose linearity across doses could not be demonstrated. The dosages that were investigated were 0.05, 0.1, 0.2, and 0.4 U/kggivenon different research days. Recently, Diasome started an 18-week (phase II/III) proof-of-concept trial in patients with type 2 diabetes who are not responding well to metformin to examine HbA1c decreases (ClinicalTrials.gov Identifier: NCT00814294). It is challenging to assess the positioning of this medicine and the effectiveness of this strategy for long-term glycaemic management due to a lack of pharmacokinetic evidence[(2)].

Capsulin: Diabetology

Diabetology (Jersey, UK) is developing capsulin, which is presently in late phase II development. It shows a peak plasma insulin

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concentration at about 80–90 min postdosing and an extended duration of action of up to 4-6 h. The larger dose (300 IU) caused a considerably bigger decline in blood glucose compared to the lower dose (150 IU) in a single dose trial including eight otherwise healthy patients with T1DM who were fasting. The mean glucose lowering was 1.6 and 0.02 mmol/l, respectively. In another trial, 16 T2DM patients received a twice-daily dosage for ten days in a capsule format (150 IU, 5.6 mg). The outcomes demonstrated that Capsulin might enhance glycaemic management with less glucose swings and PPG spikes during the day, including mealtimes. Despite the short research length, there was a noticeable improvement in weight, lipids, and HbA1c, and no hypoglycemic episodes were described[(2)].

Recent advancements in oral administration of insulin-loaded liposomal drug delivery systems for diabetes mellitus:

A spherical vesicle made up of one or more lipid bilayers is called a liposome. Phospholipids assemble themselves to create lipid bilayers. Drug molecules can attach to the vesicle's surface or be enclosed in hydrophilic lipid bilayers or the hydrophilic internal watery core due to the poor permeability. Prior research has demonstrated that liposomes may be delivered through a variety of delivery methods, including oral, pulmonary, intravascular, and ophthalmic. Liposomes appear to be a promising oral drug delivery technique in comparison to other sub-micron sized drug delivery systems due to their biocompatibility, stable bilayer membranes, protection against enzyme degradation, and cell-specific targeting. Drugs that are both hydrophilic and hydrophobic might be encapsulated in such a delivery mechanism. The ability of liposomes to encapsulate peptides, nucleic acids, antibiotics, genes, and anticancer medicines with limited therapeutic indices is perhaps its most significant feature. Encapsulating these compounds into liposomes reduces the likelihood of enzymatic breakdown and unintended immunological response[(19)].

For the purpose of delivering peptides orally, both traditional and innovative liposomes have been thoroughly studied in recent decades. While innovative liposomes are made of partially replaced phospholipid and cholesterol, conventional liposomes are made entirely of these ingredients. Generally speaking, the main suppliers of phospholipids and cholesterol are plants (such soy beans) and animals, respectively. Cholesterol is the main component of cell membranes and is present in significant concentrations in the tissues of the human brain and nerves. We will outline the current situation for liposomal formulations loaded with insulin that are delivered orally in this review, then go over the state of the art for these vesicles. An extensive summary of insulin-loaded conventional liposomes as well as innovative formulations such as surface coating liposomes, cell-specific targeting liposomes, bilosomes, liposomes containing botanic steroids, proliposomes, double liposomes, and archaeosomes will be given in this study. Finally, the development of such nanoscale drug delivery systems and its future directions for improving oral bioavailability will be covered[(19)].

Insulin-loaded liposome and its composition

There are two types of liposomes: traditional liposomes and unique liposomes. Sub-micron carriers have garnered significant interest for the encapsulation of protein and peptide pharmaceuticals. A number of variables, such as the phospholipid/cholesterol ratio, the phospholipid/drug ratio, the pH of the buffering agent during hydration, and the phase ratio of the water-in-oil emulsion, should be considered in order to optimize the particle size and entrapment efficiency of insulin into the core. A suitable ratio of cholesterol to phospholipids facilitates the creation of membrane fluidity, holds the largest possible number of insulin molecules, and prevents insulin leakage from the liposome core. The binding of medicinal molecules to the exterior surface of liposomes may also be influenced by temperature, curvature, and the makeup of the lipid bilayers.Insulin was shown to adhere better to surfaces at low temperatures and in the presence of tiny unilamellar liposomes.

A single µmol of phospholipid can bind to 40–60 µg of insulin through a hydrophobic contact. However, there are some challenges with using traditional liposomes for insulin oral administration. Novel bilosomes added bile salts such sodium glycocholate, sodium taurocholate, and sodium deoxycholate to the liposomes in order to improve the integrity, stability, GI permeability, and bioavailability of orally administered liposomes. Human hepatocytes that release bile juices include these bile salts. Previous research suggested that protein antigens, such hepatitis B and tetanus toxoid, might significantly increase systemic and mucosal immunity when provided orally as bilosomes, as opposed to parenteral vaccinations.Additionally, bile salts might prevent the GI tract's bile salts (5 and 20 mM) from

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degrading the bilosome vesicles, preserving 80–90% of the protein antigens. Bile salts may also increase the vesicles' membrane fluidity and, thus, their GI penetration.

Proliposomes were used in addition to bilosomes and ordinary liposomes for the oral administration of insulin. To create dried and free-flowing particles, proliposomes can be made by the spray drying technique or the film dispersion freeze drying method. Adsorbed to the mannitol and sorbitol particles are both medications and phospholipids. It has been shown that proliposomes enhance insulin oral bioavailability and GI absorption. Insulin molecules preferentially attach, via hydrophobic interactions, to tiny unilamellar liposomes with an uneven distribution of phospholipid and a high surface curvature as compared to big multilamellar liposomes.

The double liposome is the final kind of liposome. Lipid-coated filters with varying pore diameters can be used to filter a liposome solution, therefore creating double liposomes via the glass-filter method. In contrast to traditional liposomes, double liposomes have the ability to encase insulin and safeguard it from enzymatic destruction. In one study, normal male Wistar rats were used to assess the hypoglycemic effects of double liposomes containing insulin and aprotinin. It was discovered that the lipid content of double liposomes affected the efficacy of insulin entrapment. Insulin was more easily able to bind to the surface of the particles when the double liposomes were positively charged. Aprotinin repressed the action of trypsin and chymotrypsin in the top sections of the small intestine (duodenum, jejunum, and ileum). Following the oral injection of insulin-loaded double liposomes (20 IU/kg), rats showed a significant decrease in their blood sugar level (BSL). Nevertheless, further research is needed to determine how double liposomes affect diabetic rats' hypoglycemic levels[19].

Conventional liposomes

Compared to free insulin, conventional liposomes may shield insulin against enzymatic breakdown by pepsin, chymotrypsin, and trypsin. It should be mentioned that the oral bioavailability and hypoglycemic effect of insulin may be impacted by the standard liposome manufacturing process. For instance, liposomes generated in an acidic environment may improve the effectiveness of trapping and the absorption of insulin from the jejunum; nevertheless, no discernible BSL decrease was noted four hours after the delivery of liposomes to rats stimulated with streptozotocin. Table 2 presents the physical properties, in vitro experiments, and in vivo monitoring of standard liposomal formulations loaded with insulin. Phosphatidylethanol was a component of insulin-loaded liposomes in one study.The findings showed that anionic phosphatidylinositol and phosphatidylcholine could both encapsulate a sizable quantity of insulin. When the formulation is given to diabetic rats, the liposomes cause the blood circulation's level of insulin to rise, which is followed by a drop in BSL[4].

Still, there were several drawbacks to insulin-loaded typical liposomes made of cholesterol and phospholipid. First off, pancreatic lipase, bile salts, and acidic buffer made typical liposomes unstable. This led to poor permeability throughout the GI tract, drug carrier disintegration, and leaking of encapsulated insulin prior to GI absorption. Secondly, hydrolysis, oxidation, aggregation, sedimentation, and fusion were common problems with traditional liposomes. These undesired characteristics may damage the phospholipid bilayers' integrity, enlarge liposomes, and compromise their physical stability, all of which might limit the amount of insulin that can be administered orally. Lastly, in comparison to other sub-micron drug delivery technologies, the entrapment efficiency of insulin in liposomes was comparatively lower[20][21].

II. DISCUSSIONS AND FUTURE EXPECTATIONS:

Oral insulin replacement treatment is a popular alternative to subcutaneous injections for diabetic individuals. Finding a suitable insulin formulation is proving more challenging than expected. The pharmaceutical industry is resuming efforts to develop an oral insulin solution after decades of unsuccessful attempts.In the previous 5 years, just 4% of oral insulin articles included clinical trial reports with human data, despite extensive evidence from in vitro and animal investigations. The limited clinical data compared to published pharmacological investigations suggest that oral insulin development is still in its early stages. Recently released clinical data may include outcomes from studies done over a decade ago or stopped development.The quality of clinical trial designs is often inadequate, contributing to the low number of publications. Except for Emisphere's 3-month phase II study and Biocon's 6-month phase III trial, all given trials are early-phase, feasibility, and proof-of-concept studies with a limited number of volunteers (usually 8-12).

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Volume 9, Issue 4 July-Aug 2024, pp: 990-1002 www.ijprajournal.com ISSN: 2456-4494

While proof-of-concept trials have shown that oral insulin administration is practical and promising, there is still potential for improvement in design and data analysis[22] .

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