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Review Article

A REVIEW ON ORAL INSULIN

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ABSTRACT

Diabetes mellitus is a serious pathological condition that is responsible for major healthcare problems worldwide. Insulin is a proteinaceous hormone produced in the islets of Langerhans in the pancreas and used as a treatment in diabetes mellitus. The present mode of insulin administration is by subcutaneous route through which insulin is presented to the body in non-physiological manner having many challenges. Hence novel approaches for insulin delivery are being explored. Oral insulin is one of the most exciting areas of development in the treatment of diabetes because of its potential benefit in patient convenience, rapid insulinization of liver, adequate insulin delivery avoiding peripheral hyperinsulinaemia while potentially avoiding adverse effects of weight gain and hypoglycaemia. Challenges to oral route of in administration are: rapid enzymatic degradation in the stomach, inactivation and digest by proteolytic enzyme in the intestinal lumen and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity. Successful oral insulin delivery involves overcoming the enzymatic and physical barriers and taking steps to conserve bioactivity during formulation processing. There is still a need to prepare newer delivery systems, which can produce dose-dependent and reproducible effects, in addition to increase bioavailability.

Keywords: Diabetes Mellitus, Oral insulin.

INTRODUCTION

Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are characterized by progressive decrease in β-cell function. Pathologically, in T1DM, autoimmune destruction results in rapid loss of β-cell function, whereas, in early T2DM, the course of disease is characterized by a diminished first-phase insulin release, accompanied by the lack of prandial suppression of hepatic glucose production, subsequent increased postprandial glucose (PPG) excursions and late insulin hypersecretion. In late stage T2DM, there is a significant loss of pancreatic β-cell mass leading to very little endogenous insulin secretion. [1]

The therapy for a subject with T1DM starts with insulin, management of subjects with T2DM typically begins with the introduction of medical nutrition therapy, life style modifications and metformin. Once metformin therapy fails to provide glycemic control, a combination therapy with additional oral hypoglycemic agents (OHAs) or basal insulin is initiated. As endogenous insulin production diminishes further, multiple injections of short-acting and long-acting insulin are added to control PPG excursions. [2] Of the available therapies for management of diabetes, insulins have the advantage of being highly effective in achieving treatment goals and almost infinitely titratable with an established safety profile over years of use. [2] Among adults with diagnosed diabetes (T1DM or T2DM) 14% takes only insulin and 13% takes both insulin and oral medications. [3] However, besides control of severe hyperglycaemia, benefits of insulin therapy include improvement in insulin sensitivity [4], reduction of glucotoxicity [5] and lipotoxicity. [6, 7] There is also mounting evidence that earlier initiation of intensive insulin is desirable as it produces sustained tight glycaemic control. [8-11]

While it is clear that traditional insulin treatment can provide significant morbidity and mortality benefits in patients, in practice, a significant number of patients with diabetes fail to attain lasting glycaemic control. [12] This is because of a variety of reasons including poor compliance associated with the method of delivery (injection), late stage at which insulins are prescribed currently, the inherent complexity of initiating and managing an insulin treatment regimen by patients

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and their healthcare providers [13], hypoglycaemia and weight gain. In the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD**)** study, there was a statistically significant difference ($p < 0.001$) in hypoglycaemia and weight gain between the two studied groups: intensive therapy vs. standard therapy. A significantly larger number of patients receiving intensive insulin therapy in the ACCORD study also required medical intervention because of hypoglycaemia. [14]

To overcome these limitations and hence to facilitate early initiation of insulin therapy, several alternative methods with a more patient-friendly way of insulin administration are in various stages of development. Some of these alternate methods other than the per-oral route target peripheral tissues (muscle and fat) rather than the liver and hence, do not replicate the normal dynamics of endogenous insulin release. Per-oral delivery of insulin appears to be most desirable alternate form of insulin delivery because it targets the liver.

Current routes for Insulin delivery and their problems: The present mode of insulin administration is by subcutaneous route by which insulin is presented to the body in non-physiological manner. The subcutaneous administration of insulin has many challenges. Insulin injected subcutaneously at least twice a day as having many inherent disadvantages include local pain, inconvenience of multiple injections and occasionally hypoglycemia as a result of overdose, itching, allergy, hyperinsulinemia and insulin lipodystrophy around the injection site. In study clinical trials have shown that even on injectable insulin treatment, a significant percentage of patients fail to attain lasting glycemic control due to non-compliance. [15]

The introduction of insulin therapy was hailed as one of the therapeutic miracles of modern times, saving lives and preserving the health of millions of people worldwide. In the years since insulin was introduced, research on many fronts has resulted in significant developments in production, purification, and pharmaceutical formulation and in refinements in devices for parenteral insulin administration. Despite these advances, realizing the dream of administering insulin orally, and hence replicating physiological patterns of insulin secretion with the accompanying advantages, remains an elusive goal. Recent advances in science and technology have brought about methods to [16] overcome the barriers to absorption presented in the gastrointestinal tract and [17] protect the insulin while in transit in the harsh adverse environment of the gastrointestinal tract. This review addresses the physiological advantages that may be derived from oral insulin administration and examines the various technologies at the forefront of oral insulin delivery.

Why oral delivery of insulin?

The oral route is considered to be the most acceptable and convenient route of drug administration for chronic therapy. Insulin if administered via the oral route will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety [18] and possible infections. [19] In addition oral insulin has advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin, subcutaneous insulin treatment however does not replicate the normal dynamic of endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patient. [20, 21]

CHALLENGES TO ORAL INSULIN DELIVERY

Insulin degrades very quickly by the stomach's acidic environment and proteolytic enzymes. Insulin molecule is too large to be absorbed from gastrointestinal tract and is broken down before it is absorbed.

The possibility of delivering insulin orally is attractive, but is often limited by poor bioavailability. The poor bioavailability of orally administered insulin is attributed to its degradation or inactivation by presystemic metabolism due to highly acidic gastric fluid, gastrointestinal pancreatic enzymes and intestinal proteolytic enzymes. [22, 23]

Generally, peptide and proteins such as insulin cannot administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity. [24-26] The oral bioavailability of most peptides and proteins therefore is less than 1%. The challenge here is to improve the bioavailability to anywhere between 30-50%. [27]

Enzymatic Barrier: The harsh environment of gastrointestinal tract (GIT) causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without discrimination. [28] Insulin therefore undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin. [21, 29] Overall

insulin is subjected to acid-catalyzed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. The cytosolic enzyme that degrades insulin is insulin-degrading enzyme (IDE). [30] Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.

Intestinal absorption of Insulin: Major barrier to the absorption of hydrophilic macromolecules like insulin is that they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the blood stream. [31] In other words, insulin has low permeability through intestinal mucosa. [32] It has been found however that insulin delivery to the mid-jejunum protects insulin from gastric and pancreatic enzymes and release from the dosage form is enhanced by intestinal microflora. [33, 34] Various strategies has been tried out to enhance the absorption of insulin in the intestinal mucosa and in some cases, they have proven successful in overcoming this barrier.

Dosage from stability: During dosage form development, protein might be subject to physical and chemical degradation. Physical degradation involves modification of the native structure to a higher order structure while chemical degradation involving bond cleavage results in the formation of a new product. [21] Protein must be characterized for change in confirmation, size, shape, surface properties and bioactivity upon formulation processing. Changes in confirmation, size and shape can be observed by use of spectrophotometric techniques, X-ray diffraction, differential scanning calorimetry, light scattering, electrophoresis, and gel filtration. [35]

STRATEGIES TO SOLVE THE PROBLEMS

In the last several decades, various strategies have been employed to overcome the formidable barrier of enzymatic digestion and poor absorption to improve permeability and to facilitate absorption by concurrent administration with protease inhibitors and entrapping insulin within Micro particles, Liposomes, Ethosomes and Nanoparticles etc. Trotta et al., reported that solid lipid microparticles [36] also appear to have interesting possibilities as delivery system for oral administration of insulin. Moufti et al., were able to produce a 50% reduction in blood glucose levels in normal rats by an insulin-containing Liposomes. [37] Dobre et al., also illustrated a lowering of blood glucose levels in normal rats following the oral administration of insulin entrapped in phosphatidylcholine/cholesterol liposomes. [38]

The insulin release from the resultant dry emulsion responded to the change in external environment simulated by gastrointestinal conditions, suggesting that the new enteric-coated dry emulsion formulation is potentially applicable for the oral delivery of peptide and protein drugs. [32]

It is evident from these studies that the inclusion of enhancers/promoters and/or enzymes inhibitors and other advancements do experdite the diffusion of insulin molecule across the epithelial membrane, but achieving the higher oral bioavailability still remains an unmet need.

GENERAL APPROACHES FOR THE DEVELOPMENT OF ORAL INSULIN

Insulin that survives intact in the digestive tract has to be absorbed systemically. The gastrointestinal tract (GIT) walls are made up of single layer of tightly bound columnar cells, which form a barrier to absorption. The cells are tightly bound to one another because of the presence of hydrophobic proteins called occludins. In addition, there is a layer of mucin, a highly glycated protein, which acts like a gel filtration membrane and prevents absorption of larger molecules. [39, 40] The epithelial layer also consists of non-specific digestive protease enzyme which can also degrade proteins. [41]

Several approaches have been tried in the literature to overcome these barriers and have been well summarized in reviews by Carino and Mathiowitz [40] and in several other publications (table 1). The most common approach which has been followed is encapsulation of insulin. Nanoparticle formulations using muco-adhesive polymers such as chitosan, poly (lactic-co-glycolic acid) (PLGA), alginate have been studied extensively. The insulin encapsulated in these polymers is physically protected from enzymatic degradation and it is shown clearly that such nanoparticles cross the epithelial layer through Peyer's patches. [42] While such encapsulated insulin has been shown to cause lowering of glucose successfully in animal models, further development has not been reported. One critical disadvantage of this 'site specific' delivery and 'colonic absorption' could be the inability to correct the loss of first-phase insulin secretion.

A second approach to prevent the enzymatic degradation has been to deliver insulin along with a protease inhibitor. In one study, five different protease inhibitors were tested individually along with insulin. [54] It was found that bacitracin, sodium glycocholate and camostat mesilate promoted the absorption of insulin while soya bean trypsin inhibitor has very little effect on the absorption. The study concluded that co-administration of protease inhibitor is one possible approach to improve insulin absorption from GIT.

A third approach at the molecular level has been the derivatization of the peptide by using polyethylene glycol (PEG). This interesting approach has helped to protect the molecule from enzymatic degradation and has been shown to increase absorption. [55] This approach has been taken into the clinic and has provided multiple drug candidates.

To overcome the problem of absorption at the gut wall, several permeation enhancers (PEs) have been studied for oral insulin delivery. The most commonly tried PEs is bile salts or fatty acids for increasing the permeability across the intestinal cell walls. Salts of fatty acids like caprate, caprylate, laurate and palmitate have been tried for oral delivery of insulin and other peptides and other macromolecules. [56] A novel PE, zonula occludens toxin (ZOT), is being studied as PE for insulin and has been shown to be effective in reducing the plasma glucose Levels. [57]

CONCLUSION

Alternative routes to insulin injections are on the horizon. By replicating the physiological route of insulin secretion and absorption, oral insulin may have definite advantages not attained by systemic insulin administration, yet it may raise new concerns inherent to oral drug products that will need to be addressed. Attempts have been made to achieve oral insulin delivery using various systems. It has been proved that insulin is subjected to acid catalyzed degradation in stomach, luminal degradation in intestine, and intracellular degradation. Scientists have been able to protect the insulin delivery system from acidic environment and target it to the intestine. The maximum bioavailability of the insulin has been reported to be very low because of the poor absorption of insulin from the intestine. Limitation to the delivery of insulin have not resulted fruitful results to the date and there is still a need to prepare never delivery system, which can produce dose-dependent and reproducible effects in addition to increased bioavailability.

Approach	**Example**
Encapsulation Microparticles and nanoparticles [43-48]	Chitosan, poly(lactic-co-glycolic acid), alginate, cyanoacrylate particles, β-cyclodextrin, liposomes
Permeation Enhancers [49, 50]	Zonula occludens toxin (ZOT), fatty acid salts and esters
Protection against Enzymes [51-53]	Pegylation, enteric coated particles, pH responsive gels, protease inhibitors

Table 1. General approaches to oral delivery of insulin

Research group	**Product name**	**Formulation**	**Technology**	**Development phase**	**Action onset**	**Action duration**
Short-acting oral insulin products						
Emisphere Technologies (58, 59)	EligenTM	Tablet	Permeation enhancer (PE)	II	20 min	1.5–2 h
Nobex Technologies (60)	HIM-2	Liquid	Pegylation plus PE	Abandoned	10 min	1.5–2 h
Biocon (61)	IN-105	Tablet	Pegylation plus PE	III	10 min	1.5–2 h
Intermediate-acting oral insulin products	**Product name**	**Formulation**	**Technology**	**Development phase**	**Action onset**	**Action duration**
Coremed (62, 63)	Intesulin	Capsule	Nanoparticle Encapsulation	Preclinical	15 min	3 h

Oramed (64)	NA	Capsule	Enteric coating plus PE	II	2 h	5–6 h
Diasome Pharmaceuticals (65)	Hepatic-directed vesicles-insulin (HDV-I)	Tablet	Liposomal insulin	II/III	30 min	12–14 h
Diabetology (66, 67)	Capsulin	Capsule	PE	II	30 min	4–6 h

Table 2: Oral insulin products that have been tested in the clinic

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