SJIF Impact Factor: 3.458

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 3.
Issue: 1.
Page N. 89-98
Year: 2019

Review Article

www.wjahr.com

# ORAL INSULIN: AN OVERVIEW

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**Received date:** 05 December 2018 **Revised date:** 26 December 2018 **Accepted date:** 17 January 2019

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**ABSTRACT**

Insulin is a major protein hormone secreted by the β-cells of the pancreas and is important for the control of diabetes. Insulin is usually administered to diabetic patients through subcutaneous injection. This mode of therapy has certain inherent disadvantages such as local pain, itching and insulin lipodystrophy around the injection site. Hence, pharmaceutical scientists have been trying to design an oral delivery system for insulin. Many challenges are associated with the oral delivery of insulin, relating to the physical and chemical stability of the hormone, and its absorption and metabolism in the human body. Still approach should encourage for a better formulation of Insulin by Oral route.

**KEYWORD:** Insulin, Pepsin, carboxypeptidase-A, endopeptidase.

## Diabetes

Diabetes mellitus (just called diabetes from now on) occurs when the level of glucose (sugar) in the blood becomes higher than normal. There are two main types of diabetes - Type 1 diabetes and Type 2 diabetes.[1]

## Understanding blood glucose and insulin

After you eat, various foods are broken down in your gut into sugars. The main sugar is called glucose which passes through your gut wall into your bloodstream. However, to remain healthy, your blood glucose level should not go too high or too low.

So, when your blood glucose level begins to rise (after you eat), the level of a hormone called insulin should also rise. Insulin works on the cells of your body and makes them take in glucose from the bloodstream. Some of the glucose is used by the cells for energy, and some is converted into glycogen or fat (which are stores of energy). When the blood glucose level begins to fall (between meals), the level of insulin falls. Some glycogen or fat is then converted back into glucose which is released from the cells into the bloodstream.

Insulin is a hormone that is made by cells called beta cells. These are part of little 'islands' of cells (islets) within the pancreas. Hormones are chemicals that are released into the bloodstream and work on various parts of the body.

## Type 1 diabetes

In Type 1 diabetes the beta cells in the pancreas stop making insulin. The illness and symptoms develop quickly (over days or weeks) because the level of insulin in the bloodstream becomes very low. Type1 diabetes used to be known as juvenile, early onset, or Insulin Dependent Diabetes. It usually first develops in children or in young adults. Type 1 diabetes is treated with insulin injections and diet.[2]

## Insulin Injections

Insulin is needed in some cases if the above treatments do not work well enough. You cannot take insulin by mouth as it is destroyed by the digestive juices in the gut.

**What is Insulin?**

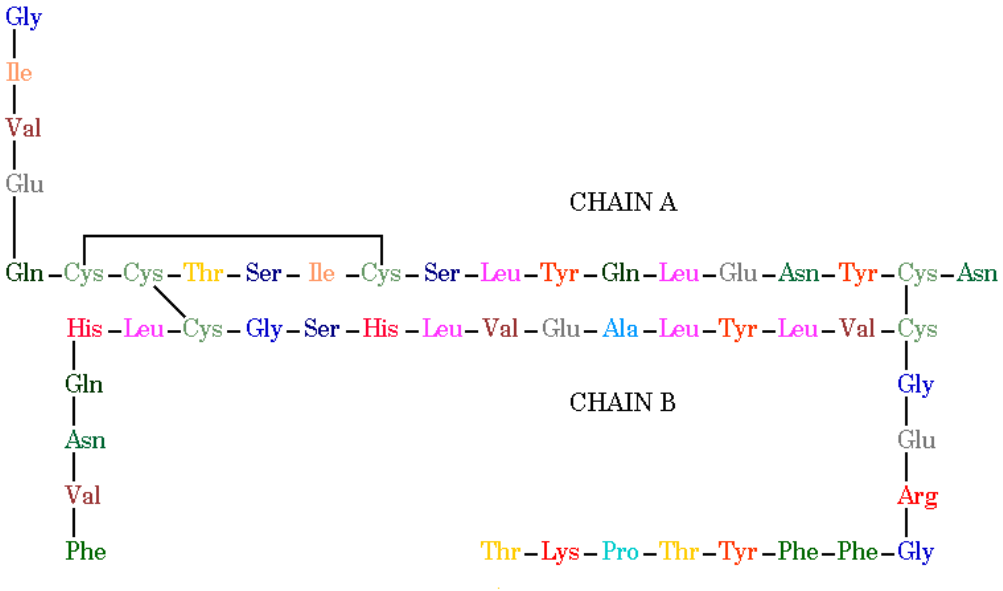


**Fig. 3: Structure of Human Insulin.**

Insulin is a hormone that your body produces to help convert the food you eat into energy. People with diabetes might need insulin injections either because they don't produce enough insulin in their bodies or they can't properly use the insulin that they do produce or both.


**Fig. 4: Humalog® KwikPen™.**

Insulin injections have come a long way since they were first used to treat diabetes in the 1920s. There are not only different types of insulin to meet each user's individual needs, but also different ways to inject insulin.

The insulin injection process itself has become easy and virtually painless, thanks to numerous innovations in BD needles, pen needles and syringes.

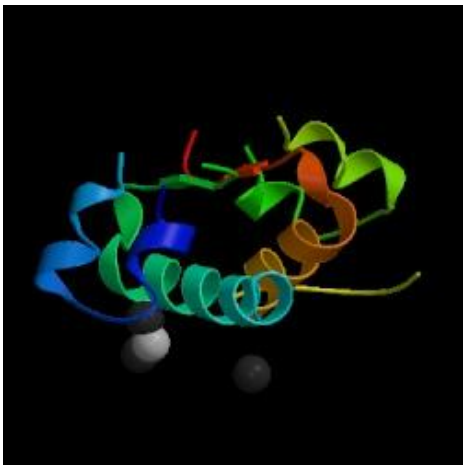

**Fig. 5: 3D structure of Insulin.**

With that in mind, we've put together an easy-to understand overview that explains how insulin therapy helps millions of people with diabetes to lead longer, healthier lives.[3]

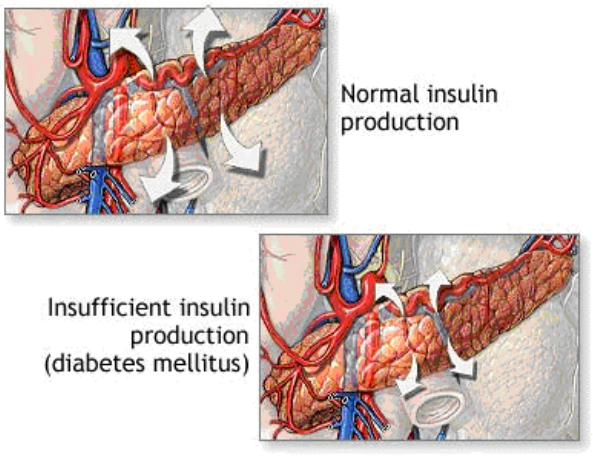


**Fig. 6: Comparison of Insulin Production.**

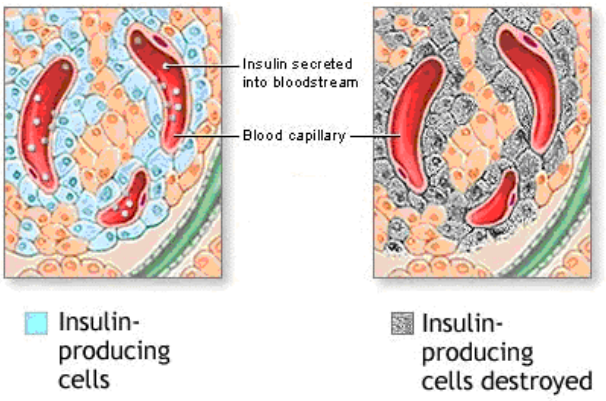


**Fig. 7: Comparison of insulin producing cells with destroyed cell.**

**Oral insulin**

**Fig. 8: Oral insulin tablets and capsules.**

Insulin is a major protein hormone secreted by the β-cells of the pancreas and is important for the control of diabetes. Insulin is usually administered to diabetic patients through subcutaneous injection. This mode of therapy has certain inherent disadvantages such as local pain, itching and insulin lipodystrophy around the injection site. Hence, pharmaceutical scientists have been trying to design an oral delivery system for insulin. Many challenges are associated with the oral delivery of insulin, relating to the physical and chemical stability of the hormone, and its absorption and metabolism in the human body. Here we discuss various strategies for the oral delivery of insulin that are being tried out, as well as methods used to improve the absorption of orally consumed insulin and to reduce its degradation by digestion. The development of an oral form of insulin has been a work in progress for many years. Many companies have decided to look for an oral form of insulin as this will help patients become more compliant with insulin therapy. They would be easier to carry around and simpler and more discreet than injecting it, so patients would be able to maintain more privacy about their need to take insulin.

Many ideas are in the works from sprays to pills. The difficulty with pills is that insulin gets easily destroyed by digestive juices in the stomach and small intestines. Finding a coating for the pill that would protect it as it traveled and dissolved once it reached the stomach was the initial problem. Also, the amount of insulin that can be put in a pill is small compared to what can be delivered in a syringe.

Insulin delivered by the oral route follows the same route to the bloodstream as insulin secreted naturally by the pancreas into the portal vein. Insulin, from the pancreas or from oral delivery, reaches the liver in high concentrations (3 times more than other tissues), activating the liver to participate in blood sugar control and regulate a number of metabolic activities that can help mitigate complications of diabetes. An oral tablet insulin product would do away with the above-cited limitations of injectable insulin, and inhaled insulin, in addition to the fact that oral delivery would have high patient compliance. Below are some companies currently trying to make this delivery process possible.

Dr. Alessio Fasano of the University of Maryland reported on research that might one day allow insulin pills to work. The report in the March, 1997 Journal of Clinical Investigation (pgs. 1158-1164), uses a protein called Zonula occludens toxin or Zot. With Zot, researchers were able to significantly increase insulin transport across the intestines to lower blood sugar levels to nearly normal levels in diabetic rats. Zot is derived from *Vibrio cholera*. This basic research has many hurdles to pass before clinical trials begin, but offers an interesting approach to the problem of protein breakdown in the stomach and intestine

Noven pharmaceuticals of Miami have developed transoral patches for delivery of anesthetics for dental work, and for treating motion sickness, angina and nicotine withdrawal. They are attempting to use similar technology to transport insulin across the membranes in the mouth. This approach faces several problems in maintaining oral healthy membranes, preventing allergies to the adhesives used, keeping the patch in place, and not having unwanted compounds or viruses also cross the oral membrane alongside the insulin.[4]

**Why oral insulin?**

Insulin injected subcutaneously at least twice a day (sometimes several injections a day) being a part of a diabetic's everyday life, can be extremely harrowing. The strict regimen diabetics must follow this mode of insulin treatment as it affects their lives to a great degree. Inherent disadvantages include local pain, itching, allergy, and insulin lipodystrophy around the injection site. Insulin lipodystrophy results in atrophy of fats at the frequent sites of insulin injection. This can be observed as irregular depressions on the skin. Lastly, clinical trials have shown that even on injectable insulin treatment, a significant percentage of patients fail to attain lasting gylcaemic control due to non-compliance.

Oral insulin making needles needless is gaining widespread prominence, to offset the above mentioned disadvantages. The oral route is considered to be the most acceptable and convenient route of drug administration for chronic therapy. Due to knowledge explosion in the biotechnology industry, extensive investigations are being conducted to achieve successful control of blood glucose by the oral delivery system.

**Research challenges**

One of the major challenges of oral insulin research has been that insulin breaks down in digestive liquids to a degree that it becomes less useful than with injecting it. The absorption of insulin is reduced in the gastrointestinal (GI) tract, due to the degradation by proteolytic enzymes (protein digesting) like pepsin. Further, the process of 'first pass metabolism' leads to a still further reduction in the bioavailability, and therefore, reduced pharmacological action of insulin. First pass metabolism is the process of detoxification that happens in the liver—contents of the small and large intestines enter the liver through the portal vein to eliminate remaining traces of toxic materials. Thus, due to enzymatic action and the first pass effect, drugs get metabolized, and are less effective.

Another oral insulin research road block is that rate of absorption from different regions of the intestine is not uniform. The cellular morphology of the intestines changes from region to region, and the proteolytic activity of protease gradually decreases from the duodenum to large intestine. Researchers suggest that there may be an optimal site for insulin administration in the small intestine, and that selective release of insulin directly into the mid-jejunum (in the small intestine) would help to protect the insulin from the gastric and pancreatic enzymes.[5,6]

**Formulation and Development of Oral Insulin**

**Fig. 9: Oral insulin capsules.**

The oral bioavailability (the fraction of the amount consumed that is actually available to the body after absorption in the gastrointestinal tract) of most peptides and proteins is less than 1%. The reasons for this are poor absorption of the drug in the gastrointestinal tract and the high likelihood of degradation by proteolytic (protein digesting) enzymes like pepsin. Moreover, any peptide or protein drug that is absorbed intact may undergo first pass metabolism in the liver. The food and drugs we consume often contain traces of toxic materials. Hence, before entering into blood circulation, the absorbed food and drugs from small and large intestines are drained into the liver, through the portal vein, and the process of detoxification then takes place in the liver. This is called first pass metabolism or first pass effect. A major portion of the drugs get metabolized through this first pass effect, and this leads to reduced bioavailability and, therefore, a reduced pharmacological action of the drug. Ever since insulin was introduced into the field of medicine, the possibility of oral administration of insulin has excited great interest. The oral route is considered to be the most acceptable and convenient route of drug administration for chronic therapy. However, for the reasons explained above, insulin delivery by this route is not as efficient as by the subcutaneous route. Absorption of proteins and peptides from different regions of the intestine is not uniform. The cellular morphology of the intestines changes from region to region, and the proteolytic activity of protease gradually decreases from the duodenum to large intestine. This suggests that there may be an optimal site for insulin administration in the small intestine, and that the selective release of insulin directly into the mid-jejunum (in the small intestine) would help to protect the insulin from the gastric and pancreatic enzymes. In the last three decades or so, hundreds of research papers on the possibilities of oral administration of insulin have been published, and the more recent attempts have explored the following options, either singly, or together: l Protecting insulin from enzymatic degradation by using antiproteolytic agents Promoting the gastrointestinal absorption of insulin through simultaneous use of a multitude of different penetration enhancers. l Chemical modification of insulin to improve its stability. l Bioadhesive delivery systems for enhancement of contact of the drug with the mucous membrane lining the gastrointestinal tract. l Carrier systems such microspheres and nanoparticles which can improve the bioavailability of insulin.

**Basis of Oral Delivery of Proteins**

It was observed that the small amount of intact protein and peptide can enter the circulation under normal circumstances. After these studies, some finding suggests that at higher peptide dosage the fraction absorbed may be expected to increase due to saturability of the degradation. These finding led the possibility of developing oral peptide delivery system.

**Potential problem associated with oral protein delivery**

The oral administration of peptide and protein drugs faces two formidable problems. The first is protection against the metabolic barrier in GIT. The whole GIT and liver tend to metabolize proteins and peptides into smaller fragments of 2-10 amino acids with the help of a variety of proteolysis enzyme (proteases), which are of four major types; aspartic protease (pepsin, rennin), cystinyl proteases (papain, endopeptidase), metallo proteases (carboxypeptidase-A, ACE) and serinyl proteases (thrombin, trypsin). The second problem is the absence of a carrier system for absorption of peptides with more than three amino acids.[7,8,9]

**Action of oral insulin**

**Site of Absorption**

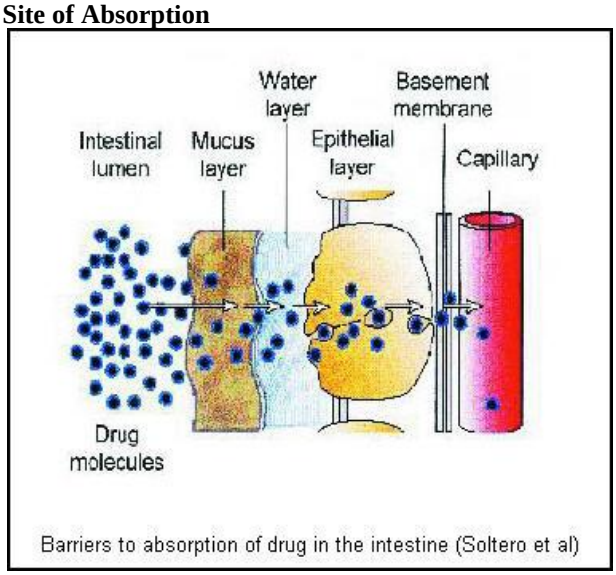


**Fig. 11: Intestinal site of absorption.**

Site-specific absorption occurs in the gastrointestinal tract because of differences in the composition and thickness of the mucus layer, pH, surface area and enzyme activity (Hammanet al. 2005). Furthermore, the Physicochemical properties of the drug not only influence the site of absorption but also the mechanism of absorption.

Despite these differences the most important site for intestinal drug absorption is the small intestine (Lacombe et al. 2004, Masaokaet al. 2006). In general, drug permeability is accepted to be higher in the upper region of the gastrointestinal tract compared to the lower parts (Masaokaet al. 2006). Timing of drug delivery is therefore important for optimized absorption and in diseases that are related to the circadian rhythm such as asthma and rheumatoid arthritis (Weidner, 2001). They concluded that the main factors affecting drug absorption are membrane permeability, luminal drug concentration and residence time in the different parts of the gastrointestinal tract, while regional pH differences are specifically important for poorly permeable drugs.

**Enteric coating**

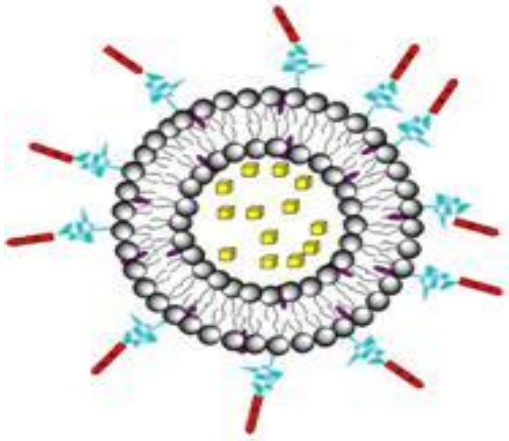

**Fig. 12: Encapsulation of insulin in liposomes.**

Enteric coating is employed to delay release of the active ingredient until it reaches the small intestine. This coating technique has been used to release drugs in the small intestine such as aspirin in order to reduce gastric irritation and erythromycin that exhibits acid degradation. Various polymers have been used as enteric polymers that become "soluble" once the pH of the environment reaches the range between 5 and 7. Polymers that degrade above a pH of 7 have been used in an attempt to target colonic drug delivery in diseases such as colitis (Gibaldi, 1984). However, the use of enteric coating to obtain colonic delivery has been reported to be less successful (Basit et al. 2004). Magnesium chloride is an example of a compound that is prone to gastric irritation due to excessive formation of hydrochloric acid in the stomach when formulated into immediate release products. Magnesium is actively absorbed from the small intestine (Reynolds, 1993) and attempts have been made to target this area by means of enteric coating. The targeting of the proximal regions of the small intestine by enteric coating has, however, been criticized because release of the active ingredient may only occur 1–2 hours after expulsion from the stomach (Basit et al.2004). This suggests release of the drug in the distal parts of the small intestine. Another potential drawback is that enteric coated tablets may be retained in the stomach for an extended period of time when taken with a heavy breakfast Ranitidine was used as a model drug to investigate differences in the bioavailability when administered in the form of immediate release, enteric coated and colon targeted delivery systems. The absolute mean bioavailability of ranitidine was found to be statistically similar for the immediate and enteric coated formulations, while it was much lower for the colonic release formulation. This was despite the fact that effective colonic release was demonstrated which was achieved by using a mixture of amylase and ethylcellose. Amylase is susceptible to degradation by amylase producing bacteria that reside in the colon (Basit et al. 2004). In this case the poor colonic bioavailability of ranitidine was ascribed to colonic bacterial metabolism.[10,11]

**Oral insulin delivery system using pH senstive polymers**

There is a growing increase in the percentage of population having diabetes mellitus due to hereditary or environmental factors. Diabetes mellitus is characterized by the destruction of the insulin secreting beta cells of islet of langerhans of the pancreas and consequent inability to maintain blood glucose level homeostasis. So diabetics must control there blood glucose levels via exogenous administration of insulin. In practice multiple injections of insulin are administered. But insulin injections cannot duplicate the physiological pattern of insulin release and at the same time it is painful and chances of infection at the site of administration are very high. The oral route is the most familiar, easy and patient friendly of all the routes of application for drug delivery. This route is not available for insulin, which is protein in nature, because it undergoes inactivation by acids and proteases in gastro intestinal tract. Moreover, the intercellular junctions of the mucosal epithelia provide the mechanical barrier to protein absorption. Taking all these factors into consideration, we have developed a pH sensitive oral insulin delivery capsule using cross-linked polymeric hydro gel based on 2-hydroxyethyl methacrylate (HEMA), poly (ethylene glycol)(PEG), methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA).

Copolymeric micro particles were found to be biostable pH sensitive and have high loading efficiency of insulin. In-vitro release of insulin was carried out by using HPLC, which showed 20% of insulin release in acidic media (pH 2.0) and 80% of insulin was released in basic media (pH-8). In-vivo experiments were carried out on diabetic rats which show significant control of blood glucose level.[12,13]

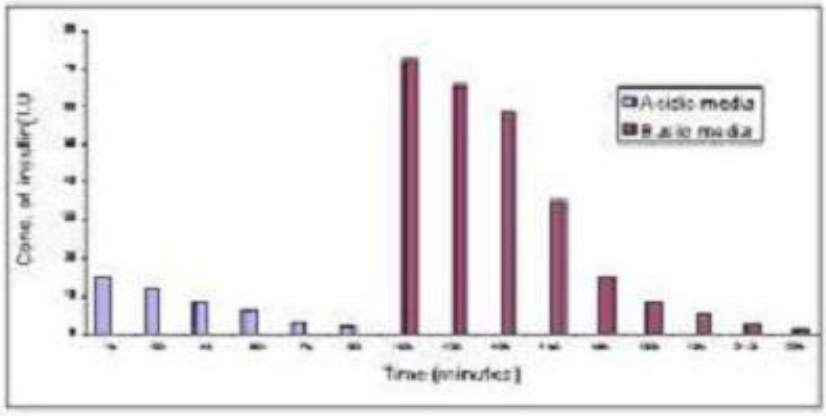


**Fig. 13: In-vitro release study of insulin from micro prous pH sensitive acrylic co-polymers peptide drugs and working of the Oral Peptide Delivery Platform.**

A peptide is a molecule made up of two or more amino acids. Large peptides, with more than 40 or 50 amino acids, are usually called proteins. The distinction is that peptides are short strings of amino acids and proteins are long strings. A significant part of food eaten is protein, for example lean meat, and the human digestive system is good at breaking protein down for absorption. This is one of the reasons peptide drugs are usually not effective when swallowed, as they are broken apart by digestive enzymes or acid in the stomach and intestines before they have a chance to be absorbed. There are 600-700 injectable peptide drugs on the market or in development, including very commercially valuable drugs such as insulin. These drugs would be more convenient and potentially more profitable if they were effective when swallowed. In 2005, the total global market for protein and peptide drugs was estimated to be US$57 billion. The combined sales of various insulin drugs amounted to US$7.3 billion, with industry analysts forecasting an increase to US$13.6 billion by 2010. The vast majority of these drugs, including insulin, need to be injected. Metabolic *Oral Peptide Delivery Platform* is based on an understanding of the structure of Metabolic drug, *AOD9604*, a peptide drug currently being developed to prevent and/or treat osteoporosis, and previously investigated for obesity. This peptide drug was found by Metabolic to be inherently orally available, which means *AOD9604* is effective even when swallowed. Around four years ago, Metabolic began exploring the hypothesis that the oral availability of *AOD960*4 resulted from the presence of a particular lipophilic (fat soluble) stretch of amino acids. This understanding led to the modification of other peptide drugs such as insulin, by attaching this lipophilic amino acid sequence. Rodent studies with various modified peptide drugs have demonstrated promising levels of oral availability (the percentage of drug which gets to the target site in the body in active form after being swallowed) ranging from 10 percent to greater than 30 percent, which is a clinically and commercially significant level.[14]

**Peptidase Inhibitors and Penetration Enhancers**

Peptidase or protease inhibitors promote oral absorption of therapeutic peptides and proteins by reducing their proteolytic breakdown by enzymes in the gastrointestinal tract. Administration of insulin via microspheres (see section on ‘Carrier systems’), together with the protease inhibitor aprotinin, has been found to be the most efficacious combination involving protease inhibitors.

Penetration enhancers can increase the absorption of peptides and proteins in the gastrointestinal tract by their action on transcellular and paracellular pathways of absorption. Penetration enhancers include substances like surfactants, fatty acids, bile salts and citrates, as well as chelators like ethylene diamine tetra acetate (EDTA). Surfactants and fatty acids affect the transcellular pathway by altering membrane lipid organization and thus increase the absorption of drugs consumed orally. Bile salt micelles, EDTA and trisodium citrate have been reported to increase the absorption of insulin. Cyclodextrins have also been used to enhance the absorption of insulin from lower jejunal and upper ileal segments of rat small intestine. A significant increase in the bioavailability of insulin can be achieved by the co-administration of protease inhibitors and penetration enhancers.[15]

**Chemical Modification**

Modifying the chemical structure of a peptide or protein is another approach to enhance its bioavailability by increasing its stability in the face of possible enzymatic degradation and/or its membrane permeation. However, this approach is more applicable to peptides rather than proteins, because of the structural complexity of proteins. For example, it is found that substitution of D-amino acids for L-amino acids in the primary structure can improve the enzymatic stability of peptides. A diacyl derivative of insulin has been seen to maintain its biological activity and also have increased absorption from the intestine.

**Bioadhesive Drug Delivery Systems and Carrier Systems**

Bioadhesive drug delivery systems anchor the drug to the gastrointestinal tract, and have been widely investigated to prepare sustained release preparations for oral consumption of drugs. The anchoring of the drug to the wall of the gastrointestinal tract increases the overall time available for drug absorption because the delivery system is not dependent on the gastrointestinal transit time for removal. Moreover, a drug administered through this method does not need to diffuse through the luminal contents (the partially digested food, etc.) or the mucus layer in order to reach mucosal epithelium lining the gastrointestinal tract. Because of intimate contact with the mucosa, a high drug concentration is presented for absorption, and there is also the possibility of site-specific delivery if bioadhesion can be targeted to occur at a particular site in the gastrointestinal tract. Bioadhesive polymers such as polycarbophil and chitosan have been reported to improve the oral absorption of insulin. Carrier systems such as nanoparticles, microspheres and liposomes can also be used to improve the oral absorption of peptides and proteins. The use of different carrier systems has been reported to improve the absorption of insulin in rats. The introduction of liposomes as a drug delivery system in the late 1980s renewed interest in the oral administration of insulin. In the following years, many investigators tested the ability of liposomes to fulfill the dual role of (1) preventing the degradation of insulin in the upper gastrointestinal tract, and (2) enhancing insulin absorption from various regions of the small intestine. The strategy of utilizing insulin loaded microparticulate systems (nano/microcapsules or particles) to circumvent the gastrointestinal enzymatic barrier and to improve absorption by the intestinal mucosa has also been tested a number of times.[16]

**Insulin patch for oral delivery**

**Fig. 14: Insulin Patch.**

A bilayered intestinal patch was designed for the oral delivery of insulin. These patches were fabricated using a mucoadhesive matrix of Carbopol, pectin and sodium carboxymethylcellulose and loaded with bovine insulin (0.25–2.50 U/mg) as a model drug. This mixture was compressed under 0.5–4.0 tons using a hydraulic press and cut into disks with a diameter of 2–8 mm and a thickness of 400 μm. Three sides of the patch were coated with a solution of ethylcellulose in acetone. The acetone was evaporated to obtain a 50 μm thick ethylcellulose backing The efficacy of the intestinal patch was evaluated in terms of insulin-induced hypoglycemia in rats, patch adhesion and insulin release. In vitro release of insulin from 4 mm diameter patches was examined in a two-chamber diffusion cell in PBS. The studies showed that insulin was released from patches for ~4 h, with 99% being released from the mucoadhesive side. In vivo insulin delivery was conducted on male Sprague Dawley rats. Three to six patches that were 2 mm in diameter and contained 0.25–1.20 U/patch were inserted in the jejunum. Alternatively, capsules containing patches with the same insulin dose, as well as 10 mg of sodium glycocholate, were also delivered by jejunal administration, rather than direct oral administration because of the large size of the capsules. Blood samples were collected from the tail vein or jugular vein and plasma insulin concentrations.[17,18]

**Factors in the oral insulin delivery route**

In the last three decades of oral insulin research, the following possibilities have been attempted and explored, either singly or in combination:

- Using antiproteolytic agents to protect insulin from enzymatic degradation
- Promoting the gastrointestinal absorption of insulin through simultaneous use of a multitude of different penetration enhancers
- Improving the stability of insulin by chemical modification
- Enhancing the contact of insulin with the mucous membrane lining of the GI tract using bioadhesive delivery systems
- Advancing the bioavailability of insulin using carrier systems such as microspheres and nanoparticles.

**Buccal insulin**

**Fig. 20: Buccal insulin.**

Several trials are testing an insulin preparation that is placed under the tongue or in between the cheek and gum, and is slowly absorbed. Generex and Eli Lilly are trying to develop an insulin spray (Oralin®) which can be delivered via the company's Rapid Mist device. The technology consists of the target molecule, excipient and non-CFC-propellant to produce a stable solution that may be rapidly absorbed from the Buccal mucosa. In a single-blind, randomized, crossover study, 11 patients with type 2 diabetes received Oralin, 15 puffs from the Rapid Mist device, or subcutaneous insulin injection, 0.11 U/kg, followed in 10 minutes by a 360 calorie meal. Oralin® outperformed subcutaneous insulin in rapidity of absorption and elimination, in glucose and C-peptide lowering capacity, and rise in serum insulin levels. A second study by the same group compared the efficacy of Oralin® in combination with oral hypoglycemic agents vs. oral hypoglycemic agents alone in a single-blind, randomized, crossover design with 13 subjects. It was concluded that Oralin can be used safely in combination with oral hypoglycemic agents to control post-prandial glucose levels. Taking it a step further, they also evaluated 22 patients with type2 diabetes and found that Oralin® spray at meals produced insulin peaks significantly greater than endogenous insulin production in patients receiving oral hypoglycemic and less post-prandial glucose elevation compared with oral insulin.

**Advantages to oral insulin**

- Reproduces the normal physiological pathway of Insulin secreted by the pancreas, that is, into the portal vein and then to the liver
- Engages the liver's full participation in the control of blood glucose
- Reduces levels of Insulin in the peripheral bloodstream, potentially decreasing the number of serious hypoglycemic events that can occur with injectable insulin therapy
- Helps ensure patient compliance.
- Oral insulin capsule suitable for type one diabetics.[19]

**Fig. 23: Insulin pills.**

**Limitations of Oral Delivery of Insulin**

A sobering fact is that in most of the above described approaches, the uptake of insulin via oral route, despite all the precautions, was less than 0.5%. A few studies performed in humans also revealed wide variation in responses to massive doses, meaning that accurate dosing is not possible. The different approaches that have been used to enhance the oral absorption and to reduce the enzymatic degradation of insulin are not infallible, and each approach has its own disadvantages and limitations.

Formulations of insulin with protease inhibitors such as aprotinin have typically shown inconsistent effects, with *in vitro* and *in vivo* effects often being different. With penetration enhancers, the in limitation is lack of specificity, which may lead to long-term toxic implications. Surfactants can cause lysis of mucous membrane and may thus damage the lining of the gastrointestinal tract. Similarly, chelators such as EDTA cause depletion of Ca2+ ions, which may in turn cause disruption of actin filaments and thus damage the cell membrane. Chemical modification does not always lead to improved oral absorption. For example, diacyl derivatives of insulin exhibited a higher proteolysis than native insulin in the small intestine of rat under *in vitro* conditions. The bioadhesive systems may be affected by the mucous turnover of the gastrointestinal tract, which varies based on site of bioadhesion. Moreover, directing a delivery system to a particular site of adhesion in the gastrointestinal tract is yet to be achieved. The

nanocapsules of insulin prepared using polyisobutylcyanoacrylate as polymeric carrier showed initial low plasma concentration followed by higher plasma concentration after sometime, with no significant net enhancement of absorption. Hence, from carrier systems, insulin gets released slowly into intestinal lumen, with small amounts being absorbed.

Thus, although techniques for developing more efficient insulation formulations are actively being pursued, it has not yet been possible to design an efficient oral delivery system for insulin. Successful delivery of insulin by oral route needs a succession of events to bypass the various penetration or enzymatic barriers. Often, to achieve this goal, a combination of two or more approaches may be required. At the present time, it is unlikely that in the short future any oral preparation that can achieve consistent, efficient and economic insulin delivery will be forthcoming.

## CONCLUSION

Among the various routes of insulin administration, each having its own set of favorable and unfavorable properties, the oral route scores over the others for the ease and comfort with which the therapeutic agent can be administered to the patient. Nevertheless some unfavorable aspects have to be circumvented to make oral insulin delivery a reality. Work on attempts to deliver insulin orally has definitely gathered momentum and is no longer considered with pessimism (18). Animal trials in the last ten years have shown that by adopting certain strategies, it is possible to achieve intestinal absorption of insulin in a physiologically active form that is sufficient to cause reduction in blood sugar levels. These include incorporation of insulin in muco (bio) adhesive polymeric carriers that would adhere to intestinal mucosa and facilitate absorption, (ii) enteric polymer coating to protect the drug as well as the carrier system from digestion in the stomach, (iii) incorporation of proteolytic inhibitors in the system to prevent insulin from intestinal enzymatic digestion, (iv) incorporation of mucous production suppressors or penetration enhancers to increase bioavailability. By using any one or a combination of these strategies, some workers were able to achieve hypoglycemic effect in diabetic induced rats. The time duration for which the hypoglycemic effect (normal blood sugar levels) could be maintained varied from few to several hours. The time point at which peak response was obtained also varied from few minutes to hours, post administration of the insulin entrapped system. Animal trials in the last decade of the past millennium have brought to limelight the strategies that hold some promise in turning oral insulin delivery from theory to reality. However the results of these studies warrant further elaborate investigations in humans. The approaches that seem to hold potential, must be consolidated and converted to a working protocol and tested in human volunteers. The results of such clinical trials only can predict whether this new millennium would witness the replacement of needles by oral insulin capsules.

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