AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Oral Insulin: Needles To Get Needless

Mir S Adil*[1], S Muzammil Hassan[2], Azizullah Ghouri[3], M Nematullah K[1], M Amer K[1], Ihtisham S[1]

1Pharm.D, Deccan School of Pharmacy, Hyderabad –01, A.P.
2Pediatrician, M.B.B.S., DCH, Princess Esra Hospital, Hyderabad, A.P.
3Deccan School of Pharmacy, Hyderabad –01, A.P.

ABSTRACT

Insulin is the most effective glucose-lowering agent, which stimulates glucose uptake in skeletal muscles, myocardium, and other tissues in order to control glucose homeostasis. Is usually administered to diabetic patients through subcutaneous injection. However, the problems encountered with subcutaneous insulin injections are pain, allergic reactions, hyperinsulinemia, and insulin lipodystrophy around the injection site. 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 and possible infections. In addition, oral insulin is beneficial because it is conveyed directly to the liver, its primary site of action, via the portal circulation, a mechanism complimentary to endogenous insulin; subcutaneous insulin treatment however does not replicate the normal dynamics of endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patients. Insulin in its present form cannot be administered through oral route. Scientists have been trying hard to design an oral delivery system for insulin by applying several approaches.

Keywords: oral insulin, diabetes, insulin tablets, hyperglycemia, novel drug delivery.

*Corresponding Author Email: iampharmd@rediff.com
Received 03 November 2013, Accepted 11 November 2013

Please cite this article in press as: Adil MS. *et al.*, Oral Insulin: Needles To Get Needless. American Journal of PharmTech Research 2013.

INTRODUCTION

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins, and an increased risk of complications from vascular disease.[1] More than 25% of the U.S. population aged ≥ 65 years has diabetes mellitus, and the aging of the overall population is a significant driver of the diabetes epidemic.[2] Type 1 and type 2 diabetes mellitus have in common high blood glucose levels (hyperglycemia) that can cause serious health complications including ketoacidosis, kidney failure, heart disease, stroke, and blindness.[3]

The classification of diabetes includes four clinical classes:

● Type 1 diabetes, which results from β-cell destruction leading to absolute insulin deficiency.

● Type 2 diabetes resulting from a progressive insulin secretory defect on the background of insulin resistance.

● Gestational diabetes mellitus (GDM) is diagnosed during pregnancy.

● Other specific types of diabetes due to other causes, such as genetic defects in β-cell function or insulin action, diseases of the exocrine pancreas and drug-induced diabetes.[4]

Moreover, metabolic abnormalities of diabetes mellitus such as hyperglycemia and hypoglycemia could have a damaging effect on the Central nervous system (CNS), which may cause seizure. [5]

Presently, the most effective glucose-lowering agent, insulin stimulates glucose uptake in skeletal muscles, myocardium, and other tissues in order to control glucose homeostasis.[6] Insulin, a protein with a molecular weight of 5808 is composed of two amino acid chains connected to one another by disulfide linkages. It is secreted by the p-cells of the islet of Langerhans. It affects the carbohydrate, protein and fat metabolism.[7]

Unfortunately insulin administration requires subcutaneous (sc) injection, which even in the simplest form is cumbersome and unacceptable to many patients with diabetes. Since the discovery of insulin in early twentieth century, attempts have been made to find the best route of administration of insulin.[8] In fact it is every patient's dream to have access to insulin without the pain of injection. Hence, some of them seek relief with oral hypoglycemic agents due to local discomfort and disruption of perceived lifestyle owing to parenteral therapy, but many patients do require parenteral insulin therapy at a later age due to exhaustion of ß cell in the pancreas.[9]

Problems of subcutaneous insulin treatment

Favorable control of diabetes depends on the patient being adapted of consistently taking accurate amounts of insulin.[10] Following are certain problems with the subcutaneous route of

insulin, which may lower the patient's quality of life:

- Insulin is not delivered in a pulsatile manner.
- Because of the delay in subcutaneous absorption, insulin is needed to be administered 30 min before meal.
- Slow return of glucose levels to the baseline after meal-time injection, therefore marked risk of hypoglycemia post insulin injection in Insulin Dependant Diabetes Mellitus (IDDM) due to over-insulinization between meals.
- The peripheral delivery of insulin rather than portal causes high plasma free insulin levels and this may accelerate the development of macrovascular disease.
- The intra-individual coefficient of variation for the time until 50% of the dose is absorbed is approximately 25% for all injected insulin.[7]
- Resistance to insulin, complexity of insulin regimes, the risk of hypoglycemia, and the chances of weight gain, as well as the necessity of a needle prick, with insulin therapy.[11]
- Insulin is presented to the body in a non-physiological manner.
- Itching, allergy and insulin lipodystrophy around the injection site are the adverse reactions due to insulin injection.[12]
- Its patient compliance is poor, owing to their phobia of needles and local pain.[6,13]
- During storage and use, insulin is degraded by hydrolytic reactions or transformed to higher molecular weight components. Hence, insulin vials should be stored under refrigeration between 2-8°C and be protected from light.[14]
- Moreover, Continuous Subcutaneous Insulin Infusion (CSII) is reported to cause unexplained mortality in the past.[15]

Consequently, oral delivery of insulin is expected to be an alternative route of administration to overcome compliance problems exhibited by the parenteral route in a better way the normal insulin pathway in the body after endogenous secretion.[13] The oral route is in general the most widely and preferred route of drug administration because it improves patient compliance. This is due to the fact that oral administration avoids the pain and discomfort as well as the possibility of infections associated with injections.[16]

However, oral administration of protein and peptide drugs is generally associated with low bioavailability (< 2%). Hence, insulin in its current form cannot be administered through oral route. The gastro intestinal tract has many physiological barriers which prevent optimal delivery of oral insulin. Physiological function of the gut enzymes is to break giant "active" proteins into

smaller "inactive" amino acids so that they can overcome the second absorption barrier "tight epithelium" in the gastro intestinal tract. These two essential barriers prevent body from potentially dangerous proteins.[11]

The poor bioavailability of these drugs can be attributed to their large molecular size, hydrophilicity and their susceptibility to enzymatic degradation. The physiology of the gastrointestinal tract also contributes to their low bioavailability due to various physical and biochemical barriers such as the physical barrier of the lipid-bilayer membranes of the intestinal epithelia, enzymatic degradation and active efflux transporter systems.[16]

Approaches towards Oral Insulin Delivery Systems:

Successful oral insulin delivery involves overcoming the enzymatic and physical barriers and taking steps to conserve bioactivity during formulation processing. In developing oral protein delivery systems with high bioavailability, various practical approaches might be most helpful:

- Protecting insulin from enzymatic degradation by using anti-proteolytic agents.
- Promoting the gastrointestinal absorption of insulin through simultaneous use of a multitude of different penetration enhancers.
- Carrier systems such microspheres and nanoparticles which can improve the bioavailability of insulin.
- Chemical modification of insulin to improve its stability.
- Bioadhesive delivery systems for enhancement of contact of the drug with the mucous membrane lining the gastrointestinal tract.[1]

Enzyme Inhibitors:

Insulin is degraded in the GIT by pepsin and other proteolytic enzymes. Enzyme inhibitors slow the rate of degradation of insulin which increases the amount of insulin available for absorption. Administration of insulin via microspheres, together with the protease inhibitors like aprotinin, trypsin inhibitors, chymotrypsin inhibitors could be found to avert the proteolytic degradation and escalate the bioavailability of insulin.

Limitations: The use of enzyme inhibitors in long-term therapy may lead to absorption of unwanted proteins, disturbance of digestion of nutritive proteins and stimulation of protease secretion.

Penetration Enhancers:

Even if the intact molecule of insulin reaches the intestine, due to the massive molecular size and relatively impermeable nature of the mucosal membrane, it might not absorb in pleasing

concentration to produce the required biological effect. One possible approach to overcome this hindrance is to use penetration enhancers. A number of absorption enhancers are available that causes these tight junctions to open transiently allowing water-soluble proteins to pass. These substances include bile salts, surfactants, trisodium citrates, chelating agents like EDTA and labrasol.

Limitations: The drawbacks with penetration enhancers include lack of specificity, i.e., they allow all content of the intestinal tracts including pathogens and toxins the same access to the systemic bloodstream and risk to mucous membranes by surfactants and damage of cell membrane by chelators.

Carrier Systems:

The oral bioavailability of insulin can be enhanced by the use of novel carrier systems which deliver insulin to the target site of absorption. Liposomes, microspheres and nanoparticles have been developed for use as carrier systems for insulin.

- *Liposomes:* These are tiny spheres formed when phospholipids are combined with water. Encapsulating insulin in liposomes results in enhanced oral absorption of insulin.
- *Microspheres:* Insulin can be encapsulated in a microcapsule or dispersed in a polymer matrix. Microspheres encapsulated with chitosan phthalate polymer protect the insulin from enzymatic degradation with an insulin-loading capacity of 62% and may be a potential carrier for oral insulin delivery.
- *Nanoparticles:* These have been extensively studied as carriers for oral insulin delivery. Nanoparticles protect insulin against in vitro enzymatic degradation. Synthetic polymers used for nanoparticle formulation include polyalklylcyanoacrylate polymethacrylic acid polylactic-co-glycolic acids (PLGA) Natural polymers used include chitosan alginate, gelatin, albumin and lectin.[1]

Chemical Modification:

Modifying the chemical structure and thus increasing its stability is another approach to enhance bioavailability of insulin. Alteration of the physicochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin.[1] Certain flavonoids have potential to increase the sensitivity of insulin receptors,[17] these can also be used to enhance insulin action.

Limitations: Chemical modification does not always lead to improved oral absorption.

Bioadhesive 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 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.

Limitations: The bioadhesive systems may be affected by the mucous turnover of the gastrointestinal tract, which varies based on site of absorption. Moreover, directing a delivery system to a particular site of adhesion in the gastrointestinal tract is yet to be achieved.[1]

Developments in oral insulin delivery:

The oral delivery of insulin has always been a significant challenge for pharmaceutical scientists. The development of oral insulin is at different stages for different companies and covers a broad spectrum from pre clinical testing to Phase II clinical trials.

Biocon is a biopharmaceutical company, developing IN-105 – a conjugated insulin molecule that is orally delivered and targeted towards liver, which is a central organ in glucose metabolism. The clinical trials for IN-105 are underway in India, USA and Europe. According to Biocon, oral insulin is simple, painless and delivered through the portal vein, mimicking the natural physiology of the body. If successful in the clinic, oral insulin could become a very important therapy for millions of patients suffering from Diabetes Mellitus (DM) worldwide.

Currently, an Israeli company, Oramed Pharmaceuticals chases a Danish pharmaceutical giant Novo Nordisk, the world's largest seller of insulin products, to be the first to produce a multibillion-dollar product. Novo is expected to be ready with the product by the end of this decade or early next. [18]

While Oramed is currently conducting Phase 2B clinical trials of its oral insulin capsule, ORMD-0801, on type 2 diabetes patients. Oramed's platform technology has two components:

- A chemical make-up that protects insulin during passage through the gastrointestinal tract, and
- Absorption enhancers so that insulin could be absorbed by the intestine.

Oramed Pharmaceuticals, Inc. through Phase 1 clinical trials, has demonstrated that its oral insulin is safe, well tolerated, and has consistently reduced glucose and c-peptide levels in

patients.[19]

Oramed's oral insulin is indicated for the early stages of Type 2 Diabetes Mellitus, when it can still slow the rate of degeneration of the disease by providing additional insulin to the body and allowing pancreatic respite. Moreover, oral insulin has the added benefit of mimicking insulin's natural location and gradients in the body by first passing through the liver before entering the bloodstream. The insulin undergoes first-pass metabolism in the liver yielding physiologically relevant insulin concentrations for systemic circulation. By such means fewer or no hypoglycemic episodes occur. This stands in sharp contrast to the sometimes fatal side effects of injectable insulin, wherein the insulin may be circulating at dangerously high doses as a result of being delivered directly into the systemic circulation, thus bypassing the body's natural metabolic mechanisms.[20]

CONCLUSION

Attempts have been made to achieve oral insulin delivery using various systems. The dream of Oral Insulin will turn into a reality in the near future with the use of superior excipients in the formulation of Oral dosage form**.** However, only further research into delivery systems can make it conceivable for the oral route to represent a feasible route of administration. Maximization of the absorptive cellular intestinal uptake and stabilization of insulin at all stages before it reaches its target will determine its final efficiency. The chances for a market launch will depend on considerable factors such as efficacy and safety as well as economic reasons. Although considerable efforts have been already made to deliver insulin orally, extensive and continuous comparison of in-vitro and in-vivo studies are essential to develop oral insulin delivery systems in the foreseeable future.

CONFLICT OF INTEREST

Authors state that there is no conflict of interest.

ACKNOWLEDGEMENT

Most importantly we are thankful to the Almighty who is the creator & director of all that initial and final modes to destiny. We take this opportunity to express our deep sense of gratitude, respect to Dr. S.A. Azeez Basha, Principal, Deccan School of Pharmacy, Hyderabad for encouraging us during the work.

REFERENCES

1. Kamlesh Wadher et al., 2009. Oral Insulin Delivery: Facts, Developments and Challenges. Der Pharmacia Lettre, 2009, 1 (2) 121-129.

2. M. Sue Kirkman et al. Diabetes in Older Adults: A Consensus Report. Journal of the American Geriatrics Society. DOI: 10.1111/jgs.12035
3. Tom L. Van Belle et al., 2011. Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies. Physiol Rev 91: 79–118, 2011; doi:10.1152/physrev.00003.2010
4. Standards of Medical Care in Diabetes—2010. American Diabetes Association. Diabetes Care, Volume 33, Supplement 1, January 2010.
5. Mir S Adil et al., 2013. Phenytoin Induced Erythematosus Rash in a Diabetic Seizure Patient. Indo-American Journal of Pharm Research 2013:3(9): 7129-7134.
6. Er-Yuan Chuang et al., 2013. Noninvasive imaging oral absorption of insulin delivered by nanoparticles and its stimulated glucose utilization in controlling postprandial hyperglycemia during OGTT in diabetic rats. Journal of Controlled Release 2013.(in press)
7. Patki and Jagasia, 1996. Progress made in non-invasive insulin delivery. Indian Journal of Pharmacology; 28: 143-151.
8. Christiane Damge et al., 1988. New Approach for Oral Administration of Insulin With Polyalkylcyanoacrylate Nanocapsules as Drug Carrier. Diabetes, Vol. 37, February 1988: 246-251.
9. Reshma D Souza et al., 2005. Nasal Insulin Gel as an Alternate to Parenteral Insulin: Formulation, Preclinical, and Clinical Studies. AAPS PharmSciTech; 6 (2) Article 27: 184-189.
10. J A H Puxty et al., 1983. Accuracy Of Insulin Injection in Elderly Patients. British Medical Journal; Vol 287: 1762.
11. Sanjay Kalra et al., 2010. Oral Insulin. Diabetology & Metabolic Syndrome, 2:66.
12. Kinesh V P et al., 2003. Novel approaches for Oral Delivery of Insulin and current status of oral insulin products. International Sciences of Pharmaceutical Sciences and Nanotechnology; vol. 3, issue 3: 1057-1064.
13. Bruno Sarmento et al., 2007. Oral insulin delivery by means of solid lipid Nanoparticles. International Journal of Nanomedicine: 2(4) 743–749
14. Vimalavathini & Gitanjali, 2009. Effect of temperature on the potency & pharmacological action of insulin. Indian J Med Res 130, August 2009, pp 166-169.
15. Lenhard and Grafton, 2001. Continuous Subcutaneous Insulin Infusion: A comprehensive review of insulin pump therapy. Arch Intern Med/Vol 161, Oct 22, 2001: 2293-2300.

16. Etienne Marais et al., 2013. Eudragit L100/N-Trimethylchitosan Chloride Microspheres for Oral Insulin Delivery. Molecules 2013, 18, 6734-6747; doi:10.3390/molecules18066734
17. Mir Shoeb Ulla Adil et al., 2013. Role of Dark Chocolate in minimising the risk of Cardio-Metabolic syndrome. Indo-American Journal of Pharm Research 2013:3(8): 6469-6476.
18. Russia might see insulin pill before America – expert. Voice of Russia, 10 October, 2013.
19. Arbit E and Kidron M. Oral insulin: the rationale for this approach and current developments. J Diabetes Sci Technol 3 (3): 562–7.
20. Official page of Oramed.