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Insulin Tablet Novel Strategy for Diabetes Management

R.P.Barkade*, P.S.Kore, Dr. S.K.Mohite & Dr. R.P.Singh
Rajarambapu College of Pharmacy, Kasegaon, Maharashtra, India

ABSTRACT:

Diabetes mellitus is a serious pathogenic condition that is responsible for major healthcare problems worldwide and costing billions of dollars. Insulin replacement therapy has been used in the clinical management of diabetes mellitus for more than 84 years. The present mode of insulin administration is by the subcutaneous route through which insulin is presented to the body in a non-physiological manner having many challenges. Despite the availability of modern insulin injection devices with needles that are so sharp and thin that practically no injection pains takes place, it is still the dream of patients with diabetes to, for example, swallow a tablet with insulin. This is not associated with any pain and would allow more discretion. Therefore, availability of oral insulin would not only easy insulin therapy, it would certainly increase compliance. However, despite numerous attempts to develop such a "tablet" in the past 85 years still no oral insulin is commercially available. Hence novel approaches for insulin delivery are being explored. Challenges to oral route of insulin administration are: rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen and poor permeability across intestinal epithelial because it's high molecular weight and lack of liphophilicity. Chitosan-coated oral tablets, Hydrogels, Cholestosomes have prepared for the oral delivery of insulin PH which can produce dose-dependent and reproducible effects in addition to increased bioavailability.

The aim of this review is to critically describe the different approaches that are currently under development.

Key words: Insulin, Oral Insulin Tablet, oral insulin pills, Chitosan-coated oral tablets, Cholestosomes, delivery Challenges, approaches.

INTRODUCTION:

Diabetes Mellitus is a common disease and its common disease in which the blood sugar level is increases above the normal sugar level and its complications are responsible for excess morbidity and mortality, loss of independence, and reduced quality of life.

Diabetes Mellitus is a serious pathologic condition that is responsible for major healthcare problems worldwide and costing billions of dollars annually.

Currents routes for insulin delivery and their problems:

The present mode of insulin administration is by the subcutaneous route through which insulin is presented to the body in a non-physiological manner having many challenges. Insulin injected subcutaneously at least twice a day is having many inherent disadvantages include local pain, inconvenience of multiple injections and occasional hypoglycemia as a result of overdose, itching, allergy, hyperinsulinemia and insulin lipodystrophy around the injection site. Because of these problem, novel approaches for insulin delivery are being explored, including oral, transdermal, nasal, rectal, pulmonary,uterine and ocular delivery as well as s.c implants. Delivery options that use dermal, nasal and oral approaches have been explored. Now days there are so many insulin products are available but they having certain limitation or disadvantages, so this review describes various insulin products and its limitations and also focus on various oral insulin delivery systems.

Why oral delivery of insulin?

The availability of modern insulin injection devices with needles that are so sharp and thin that practically no injection pains takes place, it is still the dream of patients with diabetes to, for example, swallow a tablet with insulin. 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. Insulin if administered via the oral route will help eliminate the pain caused by injections, psychological barriers associated with multiple daily injections such as needle anxiety and possible infections. Oral insulin is advantageous because it is delivered directly to the liver, its primary site of action via the portal circulation, a mechanism is a very similar to endogenous insulin.

Challenges to Oral insulin delivery:

Generally, peptides and proteins such as insulin cannot be administered via oral route due to rapid enzymatic degradations 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.

The oral bioavailability of most peptides and proteins is less than 1%.the challenge here is to improve the bioavailability to anywhere between 30-5%.

Enzymatic Barrier:

The gastrointestinal tract causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without any discrimination. Insulin is degraded by pepsin and pancreatic proteolytic enzyme such as trypsin and chymotrypsin.

Intestinal transport of insulin:

Another major barrier to the absorption of hydrophilic macromolecules like insulin is that they cannot diffuse across epithelial cells membranes to the blood stream. Insulin has low permeability through the intestinal mucosa.

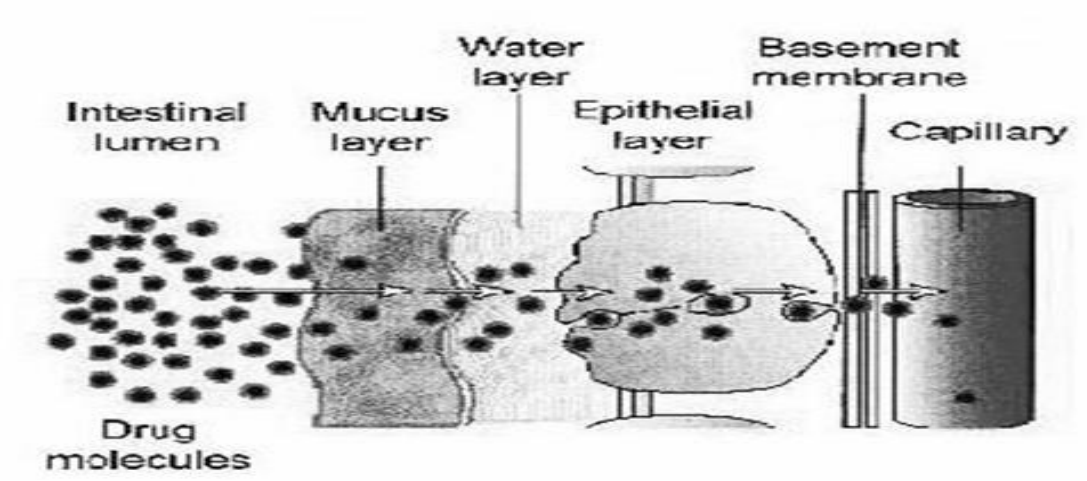

Fig.1. barriers to absorption of drug in the intestine.

Dosage form stability:

The activity of proteins depends on the three-dimensional molecular structure during dosage form development; proteins might be subject to chemical and physical degradation.

Approaches for oral insulin:

In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful.

1. Modifications of physicochemical properties such as lipophilicity and enzyme susceptibility.
2. Addition of novel function to macromolecules.
3. Use of improved carrier systems.

Enzyme inhibitors:

Insulin is degraded in the GIT by pepsin and other proteolytic enzymes. Enzymes inhibitors slow the rate of degradation of insulin which increases the amount of insulin available for absorption. The earliest studies involving enzymes inhibitors were carried out with sodium cholate along with aportinin which improved insulin absorption in rats.

Penetration enhancers:

Hydrophilic molecules like insulin are adsorbed to the apical membrane and are internalized by endocytosis. Mucoadhesive polymers have been proven to be safe and efficient intestinal permeation enhancers for absorption of protein drugs.

Chemical Modifications:

Modifying the chemical structure of a peptide or protein is another approach to enhance bioavailability by increasing its stability against possible enzymatic degradation or its membrane permeation. For example, substitution of D-amino acids for L-amino acids in the primary structure can improve the enzymatic stability of peptides.

Carrier systems:

Hydrogels:

These are cross-linked networks of hydrophilic polymers which are able to absorb large amounts of water and swell, while maintaining their three dimensional structure. complexastion of hydrogels are suitable candidates for oral delivery of proteins and proteins and peptides to changes in ph in the GI tract and provide protection to the drugs from the harsh environment of the GI tract.

Under development products of insulin:

IN -105 (Biocon, Bangalore)

This large Indian-based pharmaceutical company has taken over the oral insulin technology developed by Nobex. Biocon is developing the IN-105 conjugated insulin molecule, administered pills has polymers added at specific locations in the B chain of the insulin to prevent insulin from getting destroyed in the stomach (insulin is made up of two polypeptide chains namely, chain-A with 21 amino acids and chain-B with 30 amino acids which are held together by two disulfide bonds). Biocons R&D group has successfully developed carefully selected formulations to give consistent absorption through the intestines, delivering the glucose –lowering effect. Now days this molecule has completed phase III clinical trials.

Oral insulin pills:

Insulin administration in the form of a pills has always been an attractive concept in research.US Scientists have been developed an oral method of administering insulin that can be less painful alternative to millions of people worldwide with the diabetes who have inject themselves with the drug to manage their blood-sugar levels.

The team has successfully encapsulated insulin using Cholestosomes. It is a neutral, lipid based particle that can be administered orally with tiny vesicles that can deliver insulin where it needs go without injection. When cholestosomes reach the intestines the body recognizes them as something to be absorbed. The vesicles pass through the intestines into the bloodstream and then cells take them in and breaking them apart releasing insulin. Studies with rat showed that certain formulations of cholestesomes loaded with insulin have high bioavailability which means the vesicles travel into the bloodstream where the insulin needs to be the researchers concluded. The results were presented at the 252nd National Meeting and Exposition of the American Chemical Society (ACS) in Philadelphia, Recently.

CONCLUSION:

By considering WHO data worldwide patients of diabetes it is very essential that to develop patient compliant drug delivery system. By the efforts put by great scientist in developing insulin therapy orally seems to promising and great future ahead.

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