NOVEL APPROACHES FOR INSULIN DELIVERY: CURRENT STATUS

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ABSTRACT

Diabetes mellitus is a serious pathologic condition which is responsible for major healthcare problems worldwide and costing billions of dollars annually. Insulin replacement therapy has been used in the clinical management of diabetes mellitus for more than 84 years.

Insulin has remained indispensable in the management of diabetes mellitus since its discovery in 1921. Comparatively, a large percentage of world population is affected by diabetes mellitus, out of which approximately 5-10% with type 1 diabetes while the remaining 90% with type 2.

The present mode of insulin administration is by the subcutaneous route through which insulin is introduced into the body in a non-physiological manner having many challenges. Hence novel approaches for insulin delivery are being explored.

Challenges that have adverse effect on oral route of insulin administration mainly includes: 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.

Approaches such as liposome, micro emulsions, nanocubicle, insulin chewing gum and so forth have been prepared to ensure the oral delivery of insulin. Attempts have been made to achieve oral insulin delivery using various systems. Scientists have been able to protect the insulin delivery systems from acidic environment of the stomach and target it to the intestine.

Limitations to the delivery of insulin have not resulted in fruitful results to date and there is still a

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INTRODUCTION

Insulin is a hormone with intensive effects on metabolism and several other body systems (e.g.; vascular compliance). Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen in the liver and muscle and stops use of fat as an energy source. When insulin is absent (or low), glucose is not taken up by most body cells and the body begins to use fat as an energy source (i.e. transfer of lipids from adipose tissue to the liver for mobilization as an energy source). As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). It has several other anabolic effects throughout the body. When control of insulin levels fails, diabetes mellitus results.[1,2]

Diabetes mellitus is a common disease 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.

Diabetes develops due to a diminished production of insulin (in type 1) or resistance to its effects (in type 2 and gestational). Both lead to hyperglycemia, which largely energy causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy and changes in energy metabolism. Monogenic e.g. MODY, constitute 1-5 % of all cases.

Through more convenient drug delivery methods, pharmaceutical companies, regulatory bodies and other government institutions can introduce better diabetes care and reduce costs related to diabetic complications caused by poor compliance." At present, several methods of non-

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invasive insulin delivery, including oral, transdermal, and nanotechnology based and gene therapy-based ones are under research. Efforts are also on to develop a diabetes vaccine. One of the most promising modes of delivery under investigation is that of inhaled insulin.

CURRENTS ROUTES FOR INSULIN DELIVERY AND THEIR PROBLEMS

The present mode of insulin administration is by the subcutaneous route by which insulin is presented to the body in a non-physiological manner. 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 clinical trials have shown that even on injectable insulin treatment, a significant percentage of patients fail to attain lasting glycemic control due to noncompliance. Because of these problems, novel approaches for insulin delivery are being explored, including oral, transdermal, nasal, rectal, pulmonary, uterine, and ocular delivery as well as subcutaneous implants.

Problems

1. Enzymatic degradation of insulin

The harsh environment of the gastrointestinal tract (GIT) causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without any discrimination. Insulin therefore undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin.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).Insulin is however not subject to proteolytic breakdown by brush border enzymes[3] Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.

2. Intestinal transport of problems

Evidence of active transport for insulin was negative .Morpho-cytochemical and biochemical evidence for insulin absorption was demonstrated in rat GIT. This result was achieved by direct instillation of a solution of insulin into various parts of the GIT, followed by visualization with gold markers and immunoassay of the insulin in blood.No evidence exists for the transport of insulin by the paracellular route. Researchers found that insulin is adsorbed to the apical plasma membrane and is internalized by endocytosis. It then reaches the basolateral plasma membrane via the endosomal pathway of small vesicles and is secretes into the interstitial space.Whether the internalization is a result of the presence of insulin receptors on the surface of the epithelial cells is unclear. The presence of insulin receptors has been demonstrated in enterocytes on both the apical and basolateral sides [4,5,6]

3. Stability problems

The activity of proteins depends on the three dimensional molecular structure. During dosage form development, proteins 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. Proteins must be characterized for change in conformation, size, shape, surface properties, and bioactivity upon formulation processing. Changes in conformation, size, shape can be observed by use of spectrophotometric techniques, X-ray diffraction, differential scanning calorimetery, light scattering, electrophoresis, and gel filtration. The stability of insulin preparations has been documented in detail, and research data on the solid-state stability of proteins in dosage forms have been reviewed recently[7,8]

APPROACHES FOR ORAL INSULIN DELIVERY SYSTEMS

Generally all peptides cannot be absorbed by the GIT due to degradation by the enzymes and also less permeability in GIT .So it is most important to consider these parameters during the formulation of insulin oral dosage form. These following parameters can be managed by managing the following things:

1. Modification of physicochemical properties such as lipophilicity and enzyme susceptibility

2. Addition of novel function to macromolecules.

3. Use of improved carrier systems.

The various oral delivery systems which have been attempted to deliver insulin orally either singly or in a synergistic approach can be categorized as follows

Advances in insulin delivery

1.   Needle and syringe

A common way of administering is with the needle and syringe. Syringes come in range of capacities (1ml, 0.5ml, 0.3ml) with different needle types. Needles have very fine points and special coating to make injections pain free. (Fig. 1)

Fig.1. Image of using insulin by Needle and Syringe

2.   Insulin pens

Insulin pen injectors are convenient and discreet way of administering insulin. They have a built-in dial that allows us to determine the amount of insulin to be injected, a short needle one end and a plunger at the other. Insulin pens are particularly useful if we need to take premixed insulin.(Fig. 2)

Fig. 2. Image of insulin pens

3.   Insulin jet injectors

Insulin jet injectors offer an alternative t needles and work by sending a fine spray of insulin into the skin using a pressurized jet of air instead of a needle.(Fig. 3)

Fig. 3.Image of insulin jet injector

4.   Insulin pump

Insulin pumps are small devices of size of a pager that can be attached to our belt or placed in our pocket. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of our abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar is high. The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas.(Fig .4)

Fig4.Image of insulin pump

5.   Insulin patches

Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional

dose can be administered by pulling off a tab on the patch.(Fig .5)

Fig. 5.Image of insulin paches

6. Insulin inhalers

Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if you have a cold or asthma. The inhalers are not yet commercially available in Australia, but have been approved for use in the USA.(Fig .6)

STRATEGIES FOR IMPROVED ORAL DELIVERY OF INSULIN

Successful oral delivery of insulin involves overcoming the barriers of enzymatic degradation, achieving epithelial permeability, and taking steps to conserve bioactivity during formulation processing. The use of enzyme inhibitors, permeation enhancers, and polymer systems has been attempted to overcome these barriers. A synergistic approach usually works best.

Enzyme inhibitors

Researchers have evaluated the use of protease inhibitors with an aim to slow the rate of degradation of insulin. They hypothesized that the slow rate of degradation will increase the amount of

Fig. 6.Image of insulin inhaler

insulin available for absorption. As discussed previously, enzymatic degradation of insulin is mediated by serine proteases trypsin, a-chymotrypsin, and thiol metalloproteinase IDE. Consequently, stability of insulin has been evaluated in the presence of excipients that inhibit these enzymes. Representative inhibitors of trypsin and a-chymotrypsin include pancreatic inhibitor [9], soybean trypsin inhibitor [9,10], camostat mesylate [11], and aprotinin [12]. Inhibitors of insulin-degrading enzyme include 1,10 phenanthroline [13], p-choromericuribenzoate [13], and bacitracin [14]. Enzyme inhibitors have been associated with systemic intoxication if they are absorbed [15,16]. If they are not absorbable, then the digestion of nutritive proteins may be disturbed.

Penetration enhancers

Permeation enhancers improve the absorption of proteins by increasing their paracellular and trancellular transports. An increase in paracellular transport is mediated by modulating tight junctions of the cells, and an increase in transcellular transport is associated with an increase in the fluidity of the cell membrane. Permeation enhancers that fall into the former category include calcium chelators, and those that fall into the latter category include surfactants. Calcium chelators act by inducing calcium depletion, thereby creating global changes in the cells, including disruption of actin filaments, disruption of adherent junctions, and diminished cell adhesion. Surfactants act by causing exfoliation of the intestinal epithelium, thus compromising its barrier functions. This raises questions about the toxicity and long-term clinical use of permeation enhancers. Most literature studies on the use of these permeation enhancers have demonstrated that their enhancement is dose and time dependent. Examples of permeation enhancers used include sodium laurate and cetyl alcohol, [17] sodium cholate, [18] ethylenediaminetetraacetic acid (EDTA) , and zonula occludens toxin (ZOT) [19] clinical.

Role of polymer systems

The use of polymer systems both alone and concurrent with absorption modifiers such as enzyme inhibitors and permeation enhancers has been evaluated. In the former system, the drug is released after uptake of the polymer system intact from the GIT. In the latter system, the drug is released in the lumen before being absorbed.

ORAL INSULIN DELIVERY APPROACHES

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. Complexation hydrogels are suitable candidates for oral delivery of proteins and peptides due to their abilities to respond to changes in pH in the GI tract and provide protection to the drugs from the harsh environment of the GI tract.

Liposomes

Insulin-entrapped liposomes cause dose-dependent hypoglycemia. Researchers have prepared liposomes with varying composition by two methods: solvent evaporation hydration and solvent spherule evaporation. Liposomes containing lecithin 100 mg, cholesterol 20 mg, insulin 150 units, and tween 1% v/v were found to be most effective.

Erythrocytes

Human red blood cells have been developed as oral carrier systems for human insulin.

Nanospheres

Damge, et.al., prepared insulin-loaded nanospheres by polymerization of isobutyl cyanoacrylate (IBCA) in an acidic medium.[20]. These nanospheres displayed a mean size of 145 nm and an association rate of 1 U of insulin per milligram of polymer. These nanospheres were dispersed in an oily medium (e.g. Miglyol 812) containing surfactant (e.g. Polox-amer 188 and deoxycholic acid) and evaluated for in vitro and in vivo degradation.

Nanocubicle

A liquid formula that can be easily dispersed in water to produce particles named "Nanocubicle" was developed by Chung and coworkers [21].

Thiolated chitosan insulin tablets

The efficacy of orally administered insulin has also been improved using thiolated chitosan. 2-Iminothiolane was covalently linked to chitosan and the resulting chitosan-TBA (chitosan-4-thiobutylamidine) conjugate exhibited 453.5 ± 64.1 µmol thiol groups per gram of polymer.

Oral insulin pill

Insulin administration in the form of a pill has always been an attractive concept in research. Due to numerous limitations of this mode of insulin administration, efficacy has been hard to

demonstrate. Research has focused on overcoming these limitations by stabilizing the degradation, improving the permeability, and adding absorption promoters to protect the insulin as it passes through the stomach.

FUTURE TRENDS FOR INSULIN DELIVERY SYSTEMS

Insulin sprays, either for the nose or mouth and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome.

Islet cell transplantation

This is a recently developed surgical procedure - called the Edmonton protocol - whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent rejection of the transplanted tissue. Clinical trials continue to establish the safety and long- term effectiveness of this procedure as a means of supplying insulin.

Insulin nanopump

The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time.[22]

Gene therapy

Two recent reports describe research into gene therapy for different aspects of diabetes. These reports are in the forefront of what will no doubt be ongoing and exciting research arising from the decoding of the human genome.

Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual insulin regulation. A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new blood vessel formation in an animal model of retinopathy. It may also be used to treat macular degeneration.[23]

CONCLUSION

The advances made in insulin delivery could surely provide intensive insulin therapy regimens that can reduce the multiple daily subcutaneous injections and heavy burden of compliance on patients. Therefore preference research and investigation must go on the development of more safe and effective delivery of insulin. The development of drug delivery systems for proteins continues to be pursued actively in academic and industry circles. The success of commercial technologies and the emergence of new ones will be demonstrated only with time. An oral delivery system of insulin will have tremendous benefits in terms of a decreased number of injections for diabetic patients and a reduced incidence of side effects.

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