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Novel approaches in Insulin Drug Delivery – A Review

Sosa George [1]

Anitha Roy[2]*

[1]II B.D.S student, Saveetha Dental College, Chennai, India
[2]Faculty of Pharmacology, Saveetha Dental College, Chennai, India

Corresponding Authors:
Anitha Roy
Saveetha Dental College,
Chennai, India
Email-
anitharoypeeter@yahoo.co.in

Abstract:
Diabetes mellitus is a chronic metabolic disorder caused by the deficiency of pancreatic hormone insulin (Type1 diabetes mellitus) or due to the resistance of cells to insulin secreted by the body (Type 2 diabetes mellitus). It is a rapidly increasing serious condition which evokes a lot of global concern. Exogenous insulin administration is a commonly used treatment for Type 1diabetes mellitus and for gestational diabetes. The conventional subcutaneous insulin injections cause a lot of suffering to the patient primarily due to pain and secondarily due to dose sensitivity and further complications. Hence alternate delivery systems are an area of endeavor for medical professionals and a convenient alternative system will be a boon to the patients. As a result of the technological advances, various invasive and non-invasive delivery systems have been introduced in the past years. Nanotechnology, particle mediated delivery, pulmonary delivery, buccal spray etc. are the most recent advances. This article reviews some of these novel delivery systems of insulin.

Keywords: Diabetes, Insulin, Insulin inhalers, Oral delivery, Transdermal delivery, Insulin devices

Review Paper

Introduction:

Diabetes Mellitus is a chronic disease of impaired glucose metabolism characterised by hyperglycaemia with altered carbohydrate, fat and protein metabolism.[1] It is of two types. Type 1 Diabetes Mellitus which is due to the atrophy of pancreatic β cells, causes insufficient insulin secretion and thus leaves the patient completely dependent on exogenous insulin supply for his survival; and type 2 diabetes mellitus, in which peripheral cells become resistant to the insulin secreted by the patient's body. Selective individuals with type 2 diabetes mellitus or those at a later stage of type 2 diabetes mellitus require exogenous insulin supply.[3] The hormonal changes during pregnancy causes glucose intolerance in some women. This is caused due to the resistance of peripheral cells to insulin. This condition is called as gestational diabetes mellitus and this condition usually reverses after delivery. In a few cases this condition persists for lifetime.[4] Insulin therapy, which is the exogenous supply of insulin is highly effective in regulating blood glucose level in diabetes patients. The reports of WHO show that, around 9% of adults aged 25 years and over, around the world had raised blood glucose levels in 2008.

Insulin is supplied conventionally through subcutaneous route. In the early days, impurities present in bovine insulin led to many immunological reactions. As a result of the advancements such as recombinant DNA technology, more purified forms of insulin is available today.[5] Subcutaneously administered insulin will get absorbed through capillaries slowly. The onset of action is slow (2-3 hrs) and the action lasts for about 6-8 hours.[2] The major drawback of insulin therapy is their invasive nature.[3] Injection associated pain, frequent dosing, social stigma

and scheduling difficulties are feared by the patient. Weight gain is another major concern, particularly among women.[6]

The disadvantages of subcutaneous insulin delivery have inspired the research for new delivery systems and hence we have many different invasive and non-invasive delivery systems available today. Oral, buccal, pulmonary, transdermal, rectal and ocular routes of insulin delivery, nanotechnology-based and gene therapy-based insulin delivery systems, implantable insulin pumps, pen devices, insulin inhalers etc. are the recent advances in Insulin therapy. Vaccine for preventing diabetes mellitus is also under research.

INSULIN INHALERS

It is a non-invasive, well tolerated delivery system, which is effective for both type 1 and type 2 diabetes mellitus. The glycaemic control by this method is comparable to subcutaneous route and it also enhances patient satisfaction, quality of life and acceptance for Intense Insulin Therapy in a diabetic patient[7]. The aerosolized insulin has a diameter of about 3µm which enhances the alveolar disposition and low oropharyngeal and large airway disposition. The onset of action following systemic absorption is about 20 minutes, which is rapid. The action lasts for about 6-8 hours, which is comparable to that in subcutaneous administration. Exubera was the first inhaled insulin preparation available. It was delivered with an aerosol devise called exubera inhaler. Nebulizers, metered dose inhalers and aqueous mist inhalers are being investigated. Inhalation is an excellent mode for delivering pre-meal time insulin. It can be used for delivering fast acting insulin only. It is less effective in smokers and those with pulmonary diseases. The incidence of hypoglycaemia is also increased with this route.[6,8]

BUCCAL DELIVERY OF INSULIN

Mucosal membranes of the inner lining of cheeks can act as excellent sites for insulin delivery .The area is robust, rich in blood supply, has expansive smooth muscle and provides short cellular recovery following damage or injury[1,2]. Visibility and accessibility of buccal mucosa also makes it an ideal site for delivery. The insulin sprayed into buccal mucosa cannot enter deep lungs because of its size and hence it is safe for lungs.[9] Insulin which is administered through buccal route is called buccal insulin, when it reaches the systemic circulation.[1] The main disadvantage of this route is the lower bioavailability due to the relatively low passage of active agent across the mucosal epithelium. Bio adhesive polymers can be used as an alternative. They adhere to the biological substrate to provide continued contact of the agent with the site of delivery. The various bio adhesive formulations include gels, films, tablets, vesicles, nanoparticles and sponges. They are retained for longer time and hence show improved pharmacokinetic as well as absorption properties. Gels, transferosomes, pelleted nanoparticles, tablets, patches, films, sponges, sprays etc. are the currently available buccal delivery formulations.[1,2]

PULMONARY DELIVERY OF INSULIN

Insulin can be administered by pulmonary route using two techniques - aerosol inhalation and intratracheal instillation. Aerosol offers more uniform distribution with greater extent of penetration into peripheral or into alveolar region of the lungs.[10] When delivered into the lungs, they are readily absorbed through the alveolar region

directly into blood circulation. This can be achieved by liquid nebulizers, aerosol based metered dose inhalers and dry powder dispersion devices. Simplicity of self administration, large surface area of lungs that improves absorption, relatively high bioavailability and non-invasiveness are the advantages of this delivery system.[2]

ORAL DELIVERY OF INSULIN

An oral dosage form is the preferred form of delivery because of the ease of administration, patient compliance and economical issues. No oral preparations of insulin are available till date .The advantage of this route of insulin delivery is the capability of insulin to mimic normal physiological role. Thus it can become more efficacious in glucose homeostasis.[5] The difficulties encountered in the oral delivery of insulin include degradation of the protein at lower pH of stomach and by different digestive enzymes in stomach and small intestine. This causes a decrease in bioavailability as low as ≤0.5%.[3,11] The variation in permeability across GIT for insulin and stability issues of the dosage form are the other major challenges for oral insulin delivery.[5] Several gastrointestinal patch systems are available today and they provide bio adhesion, unidirectional release and protection for the drug from pH variations and also from enzymes. This combination of functions improve bioavailability of large sized molecules.[2] Protection of insulin from gastric environment has been achieved by coating the nanoparticles with pH sensitive polymers, which will dissolve in the mildly acidic environment of the intestine.[3] Complexation hydrogels significantly enhance oral absorption of insulin with notable hypoglycaemic effect.[12] Recombinant human insulin can be delivered by using niosomal formulations.[13]

TRANSDERMAL DELIVERY OF INSULIN

It is a needle free technique, which is convenient with good patient compliance and prolonged therapeutic application. It bypasses first pass metabolism and escapes degradation by gastric enzymes. Iontophoresis is a technique that improves the transdermal delivery of compounds through skin by application of a small amount of electrical current. Microdermabration is another method that improves the permeability of insulin through skin. It is achieved by mildly damaging or removing the outer layer of skin, stratum corneum[3].

INSULIN DEVICES

Insulin infusion devices may be classified as open-loop and closed-loop systems. Programmable open-loop micropump insulin delivery device consists of a small, lightweight, portable insulin micropump and a plastic tubing which connects the pump to a needle inserted under the skin. Insulin release patterns in them can be pre-programmed and initiated by timer or by the diabetic patient himself. This device demands a very careful monitoring of blood glucose level. Also the patients using these devices were reported to show high incidence of ketoacidosis. Implantable versions of open loop insulin infusion devices were also introduced. Chemically controlled closed loop insulin delivery devices work by feedback mechanism. It is an effective alternative in the absence of an effective pancreas or β-cell transplantation. It mimics pancreatic activity. They are biocompatible and non-toxic. The biohybrid artificial pancreas is another type of insulin diffusion device, which is under research. These contain β-cells enclosed within a semi permeable membrane, which is biocompatible. The semi permeable membrane is

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permeable to glucose and insulin. Special has to be given to exclude immune cells in order to prevent rejection by the body.[14-16]

INSULIN DELIVERY USING PEN DEVICES

It is a convenient and accurate method of insulin delivery. Its goal is to improve glyceamic control by making it less difficult to follow the current recommendations for intensive insulin regimens. Two types of pens are available; prefilled and reusable. Pens are available in various styles. Insulin pens have the potential to become a major asset for the improved compliance among all patients undergoing insulin therapy.

OTHER NOVEL METHODS IN INSULIN DELIVERY

Erythrocytes, which are the most abundant cells in the body, can be used as effective carriers of many different drugs including insulin. Biocompatibility, biodegradability, long circulation half life and the ability to get loaded with a variety of chemically and biologically active compounds make resealed erythrocytes excellent carriers of therapeutic agents.[17] Dendrimers are macromolecules with highly branched 3D structure.[18] They also are used for successful delivery of insulin.

CONCLUSION

The research and advancements in insulin delivery is really promising. There are many issues which make the patient hesitant to initiate insulin therapy. So, many alternative routes for insulin delivery are under research and some of them are available. Each one has its own advantages as well as drawbacks. A suitable alternative, with high efficiency and good patient compliance is likely to emerge in future to help out people with type1 diabetes, gestational diabetes and type 2 diabetes not controlled with oral hypoglycaemic agents.

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