Review Article

NANOPARTICLE INSULIN DRUG DELIVERY-APPLICATIONS AND NEW ASPECTS

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder caused via the deficiency of pancreatic hormone insulin (Type1 diabetes mellitus) or due to the resistance of cells to insulin secreted by using the body (Type 2 diabetes mellitus). It is a rapidly growing serious situation that inspires a lot of global concern. Exogenous insulin administration is many times used therapy for Type 1 Diabetes Mellitus and gestational diabetes. The traditional subcutaneous insulin injections cause a lot of suffering to the affected person, exceptionally due to pain and secondarily due to dose sensitivity and in additional complications. Hence alternate delivery systems are an area of recreation for medical professionals and a convenient alternative system will be a boon to the patients. As an end result of the technological advances, various invasive and non-invasive delivery systems have been brought in the previous years. Nanotechnology, particle-mediated delivery, pulmonary delivery, buccal spray, etc. are the most current advances.

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

INTRODUCTION

Diabetes Mellitus is a chronic disease of impaired glucose metabolism characterized by using hyperglycemia with altered carbohydrates, fats, and protein metabolism. It is of two types. Type 1 Diabetes Mellitus which is due to the atrophy of pancreatic β cells, motives inadequate insulin secretion and as a result leaves the affected person completely dependent on exogenous insulin supply for his survival; and type 2 diabetes mellitus, in which peripheral cells grow to be resistant to the insulin secreted via the patient's body. Selective individuals with type 2 diabetes mellitus or these at a later stage of type 2 diabetes mellitus require exogenous insulin supply. The hormonal adjustments for the duration of being pregnant motivate glucose intolerance in some women. This is brought on due to the resistance of peripheral cells to insulin. This situation is referred to as gestational diabetes mellitus and this situation commonly reverses after delivery. In a few cases, this circumstance persists for a lifetime.4 Insulin therapy, which is the exogenous supply of insulin, is highly effective in regulating blood glucose levels in diabetes patients. DM reasons considerable rates of morbidity and mortality to the current population [1].

Insulin is used to manage the level of blood glucose in sufferers with DM. It is a quintessential therapy for patients suffering from T1DM, and T2DM (especially in late-stage disease). Insulin was once discovered in 1921 by Frederick Banting and Charles Best, went through its first scientific use in 1922 [2-4], and helped revolutionize the cure of T1DM, which was once deadly at that time. Initially, insulin was once isolated from bovine and porcine pancreata, till the 1980s. Later on, recombinant DNA strategies allowed the manufacture of human insulin. Modifications of the amino acid sequence of the insulin molecule using rDNA and protein engineering strategies have currently allowed the manufacturing of monomeric insulin analogs (e. g. lispro, aspart) which have a more rapid absorption profile [3].

Since DM results in a defect in insulin function, the perfect therapy is to permit diabetics to regain normal insulin function. However, present-day research and technology have no longer been capable to obtain this. The present-day insulin therapy includes exogenous administration to accomplish effective glycaemic manage (i.e. prevention of hyper-and hypoglycemia) and avoidance of the issues of DM [5]. Current modes of delivering insulin include intravenous (IV) infusion and subcutaneous (SC) injections. SC insulin preparations, which are greater typically used, include rapid-, intermediate-and long-acting insulin, which are used in extraordinary combos (1 to 4 times or more daily) [3].

Disadvantages of presently authorized insulin regimens relate to the injectable mode of its administration. Daily injections have led to non-compliance, which has apparent effects on patient outcomes. Also, parenteral administration bypasses the liver, unlike physiologically-secreted insulin. Hepatic first-pass metabolism, which decreases the quantity of circulating insulin via about 50% in normal individuals, prevents peripheral hyperinsulinemia and its related complications [5-11].

Delivery route of insulin

Oral delivery

Insulin remedy is correctly used in the therapy of diabetes mellitus. Insulin is a key participant in decreasing blood glucose levels for type 1 diabetes and is additionally required at later stages in type 2 diabetes patients. The extensively common route for delivery of insulin usually is through parenteral administration however, this delivery of insulin usually requires at least three or 4 daily insulin injections for good glycemic control. Consequently, more acceptable distinctive routes of insulin delivery have been searched to minimize suffering from discomfort, local pain, irritation, infection, immune reactions, and lipoatrophy at the injection website of insulin. Oral delivery of insulin would deliver the drug directly into the liver via portal circulation and ought to mimic the physiological destiny of endogenously secreted insulin [12-14]. However, polypeptides, like insulin, are degraded in the stomach pH and undergo proteolysis using enzymes in the gastrointestinal tract [15, 16]. Moreover, the gastrointestinal mucosa has low permeability for large hydrophilic peptides.

To overcome the issues related to parenteral administration of insulin numerous techniques that are primarily based on nanotechnology has been developed to decorate the intestinal absorption of different protein and peptides. NPS consist of naturally taking place biodegradable polymers is extensively investigated in this regard. They have emerged as potential carriers of various therapeutic agents for managed drug delivery as well as the oral route of insulin. Various natural hydrophilic and hydrophobic polymers used as the carrier of oral insulin such as chitosan, alginate, dextran sulfate, etc. are normally used to prepare NPs.

Polymers used as media for oral insulin delivery

Over the previous few decades, improving interest has been paid to the use of polymeric NPs, either hydrophilic or hydrophobic as

carriers for insulin delivery. Hydrophilic polymers are of unique activity due to their non-toxic, biocompatible, biodegradable, and herbal polymers. Among them, chitosan is extensively used due to the fact of its ease of chemical change and promising biological properties.

Hydrophilic polymers

Chitosan (CS)

CS is a well-known naturally occurring copolymer of beta-linked and N-acetyl glucosamine and has been generally found in crustacean (crabs, shrimps, and lobsters) shell and some fungi or yeast. It is a biodegradable, biocompatible, non-toxic, non-allergic, easily absorbable natural hydrophilic polymer properties that have resulted in a wide array of applications in biomedical and drug delivery research [17, 18]. It has also been shown as a paracellular permeability enhancer by interacting with the TJ proteins occluding ZO-1 and opens the tight junctions between epithelial cells [19, 20]. In addition to these properties, it increases the stability of nanospheres and facilitates effective encapsulation of proteins and drugs that make it a suitable carrier material [21, 22]. CS has been extensively used to develop new chitosan derivatized polymers. *In vivo*, preclinical research of this formulation at a dose of 30 IU/kg in streptozotocin (STZ) induced diabetic rat models confirmed extended intestinal absorption of insulin from γ-PGA NPs. It has obtained a long-lasting hypoglycemic effect and 15% relative bioavailability in contrast to subcutaneous (sc) injection [23]. The identical system filled in enteric-coated capsules used to be even higher at the identical dose, showing 20% oral bioavailability. Also, as section insulin (=monomeric, 3 times quicker than regular) is encapsulated in the equal CS-γ-PGA; it has got 15.7 % oral bioavailability [24].

Moreover, insulin-loaded NPs with carboxylated chitosan and Poly-methyl methacrylate (PMMA) had been developed to enhance insulin delivery through the oral route. One of the most broadly investigated polymers in the direction of peptide delivery is acrylates which have excessive interest due to the fact of its pH sensitivity and carboxyl groups to enhance the bioadhesive, alter the tight junction, chelate the Ca2+thereby inhibiting the proteolytic activity of proteases, etc. They evaluated their capacity to decrease blood glucose levels in diabetic rats. *In vivo* experiments resulted in the reduction of blood glucose levels through 67% at a dose of 100 IU/kg and the pharmacological bioavailability of the 25 IU/kg at a dose of PMMA NPs was once 9.7% [25, 26].

Chitosan with sodium alginate is being organized as another insulin loaded nanoparticle product which is used to enhance the loading ability and activity maintenance. It's observed that when insulin-loaded nanospheres (25, 50, 100 IU/kg) administered orally to diabetic rats they decreased glycemia in a dose-dependent manner. Their pharmacological availabilities are found 7.1, 6.8 and 3.4 %, respectively [27, 28].

Dextran sulfate-vitamin B12

Dextran sulfate is a non-toxic and highly water-soluble distinctive polymer used as matrices for oral delivery of insulin. Vitamin-B12 is proven as a ligand to enhance the uptake of the dextran NPs and their translocation throughout the gastrointestinal tract for excessive bioavailability. Insulin conjugated to dextran-vitamin B12 NPs to diabetic rats that had the least quantity of cross-linking was most effective at reducing blood glucose levels (70-75%) in STZ brought on diabetic rats. Also, the hypoglycemic impact lasted for 54 h. This amendment confirmed the best hypoglycemic effect with a pharmacological availability of 29.4% [29, 30].

Hydrophobic polymers

Poly (lactide-co-glycolide) (PLGA)

Particles consisting of PLGA have been extensively studied as therapeutic delivery vehicles owing to their biodegradable and biocompatibility particles. The hydrophobic nature of PLGA matrices typically makes them incapable of entrapping water-soluble insulin. Intragastric administration of the insulin-loaded PLGA NPs (20 IU/kg) to diabetic rats decreased fasting plasma glucose levels to

57.4% inside the first 8h of administration. The relative bioavailability of insulin following oral administration of NPS used to be 7.7% in contrast to the subcutaneous injection of its solution. Star-branched PLGA (β-cyclodextrin-PLGA) NPs are highly promising for mitigating the burst impact and prolonging the release of insulin. Another study attempted to prevent the burst release of insulin in the stomach with the aid of the usage of a cellulose derivative (hydroxypropyl methylcellulose phthalate, HPMCP) to prepare PLGA NPs. This modification decreased the preliminary release of PLGA NPs in simulated gastric fluid from 50% to 20%, and their relative bioavailability in diabetic rats was once approximately 6.2% [31, 32].

Polylactide acid (PLA)

PLA showcases a strong affinity towards the small intestine due to their polyethylene oxide (PEO) blocks and an excessive permeation functionality towards the cell membrane owing to their amphiphilic property. When orally treated with vesicular PLA NPs loaded with insulin to diabetic mice (50 IU/kg), the highest blood glucose discount was once achieved at 4.5 h. Although this effect lasted at least an extra 18.5 h, growing the insulin concentration to 100 IU/kg did no longer enhance this hypoglycemic effect (hypoglycemic effect lasted for 23 hr) [33].

Poly-ε-caprolactone (PCL)

NPS organized with PCL and a monomeric form of insulin analog (aspart-insulin). Their outcomes demonstrated that this method permits for the protection of biological activities of insulin, an expansion of serum insulin levels, and enhancement of the glycemic response. The most impact of a reduction in hyperglycemia used to be found at 8 h after oral administration, which used to be more pronounced with aspart-insulin-loaded NPs (52%) at the dose of 50 IU/kg [34].

Lipidic polymers

[Solid lipid NPS (SLN)]

Previous research has demonstrated that nanoencapsulation of proteins in SLNs prolongs their blood residence time, modifies their redistribution, and improves their bioavailability [35]. Oral insulin delivery with SLNs administered to diabetic rats; their relative pharmacological bioavailability used to be 5.1% in contrast to SC injection of insulin; a considerable hypoglycemic effect used to be additionally observed during 24 h. To facilitate the transport of particles throughout the cellular barriers, in another study, the relative bioavailability extended to 7.1%.

Insulin inhalers

It is a non-invasive, well-tolerated delivery system, which is positive for each type 1 and types 2 diabetes mellitus. The glycaemic control via this approach is related to the subcutaneous route and it additionally enhances patient satisfaction, quality of life, and acceptance for Intense Insulin Therapy in a diabetic patient7. The aerosolized insulin has a diameter of about 3μm, which enhances the alveolar disposition and low oropharyngeal and giant airway disposition. The onset of action following systemic absorption is about 20 min, which is rapid. The action lasts for about 6-8 h, which is related to that in subcutaneous administration. Exubera was once the first inhaled insulin education available. It was once delivered with an aerosol device known as an Exubera inhaler. Nebulizers, metered-dose inhalers, and aqueous mist inhalers are being investigated. Inhalation is a remarkable mode for delivering pre-meal time insulin. It can be used for delivering fast-acting insulin only. It is much less wonderful in people who smoke and these with pulmonary diseases. The incidence of hypoglycemia is additionally elevated with this route [36, 37].

Buccal delivery

Mucosal membranes of the internal lining of the cheeks can act as remarkable sites for insulin delivery. The area is robust, rich in blood supply, has expansive smooth muscle, and gives brief cellular restoration following injury or injury. Visibility and accessibility of buccal mucosa additionally make it the best site for delivery. The

insulin sprayed into buccal mucosa can't enter deep lungs due to the fact of its size and subsequently, it is secure for lungs.9 Insulin which is administered through the buccal route, is known as buccal insulin when it reaches the systemic circulation.1 The most important drawback of this route is the decreased bioavailability due to the extraordinarily low passage of active agents throughout the mucosal epithelium. Bioadhesive 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 quite several bioadhesive formulations consist of gels, films, tablets, vesicles, nanoparticles, and sponges. They are retained for a longer time and as a result, exhibit improved pharmacokinetic as well as absorption properties. Transferosomes Gels, patches, pelleted nanoparticles, tablets, sprays, films, sponges, etc. are the presently accessible buccal delivery formulations [38, 39].

Pulmonary delivery

Insulin that can be administered via a pulmonary route the usage of two methods-aerosol inhalation and intratracheal instillation. Aerosol presents a more uniform distribution with a greater extent of penetration into the peripheral or into the alveolar region of the lungs [40]. When delivered into the lungs, they are readily absorbed via the alveolar region directly into blood circulation. This can be completed via liquid nebulizers, aerosol-based metered dose inhalers, and dry powder dispersion devices. The simplicity of self-administration, the large surface area of lungs that improves absorption, exceptionally excessive bioavailability, and non-invasiveness are the benefits of this delivery system [39].

Insulin devices

Insulin infusion devices may also be categorized as open-loop and closed-loop systems. Programmable open-loop micropump insulin delivery system consists of a small, lightweight, transportable insulin micropump and plastic tubing that connects the pump to a needle inserted below the skin. Insulin release patterns in them can be preprogrammed and initiated by using the timer or via the diabetic affected person himself. This device needs very careful monitoring of blood glucose levels. Also, the patients using these devices have been suggested to exhibit an excessive incidence of ketoacidosis. Implantable variations of open-loop insulin infusion units have been additionally introduced. Chemically managed closed-loop insulin delivery devices work by way of a remarks 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 any other type of insulin diffusion device, which is beneath research. These contain β-cells enclosed inside a semi-permeable membrane, which is biocompatible. The semi-permeable membrane is permeable to glucose and insulin. Special has to be given to apart from immune cells to forestall rejection utilizing the body [41-43].

Transdermal delivery

Transdermal insulin delivery is an attractive choice to the invasive parenteral route of administration and different alternative routes of insulin such as pulmonary and nasal routes due to the fact the skin provides the benefits of easy access and a very massive surface area. It improves patient compliance and avoids each liver's first-pass metabolism and the degradation of drugs in the gastrointestinal tract. The pores and skin additionally represent a vital painless interface for systemic drug administration. Despite these benefits, the human pores and skin limit the permeation of foreign compounds particularly large hydrophilic molecules like insulin. The stratum corneum; which is the top layer, reasons the impermeability of the skin by way of its lipid-rich matrix. Several attempts have been made to overcome the pores and skin barrier and to enable the transfer of large drugs such as insulin. They can be divided into chemical (liposome and chemical enhancers) and physical techniques (mainly iontophoresis and sonophoresis).

Transdermal delivery methods

Chemical enhancers such as surfactants, fatty acids, fatty esters, and azone-like compounds alter the lipid shape of the stratum corneum.

They minimize its barrier properties and enhance its permeability for massive molecule drugs that would not pass via the skin.

Iontophoresis is a non-invasive approach used to enlarge transdermal insulin penetration through the pores and skin by using the application of a small electric current potential. Large drug molecules can be delivered in a shorter time with the assist of this technique and it will increase drug mobility.

Another non-invasive method sonophoresis (ultrasound, phonophoresis) which has been used to enhance (and or delivery and activity of drugs) pores and skin permeability to a number low and high molecules weight drugs such as inulin. Low-frequency ultrasound (20-160 kHz) decreases blood glucose levels both in animal and human studies [44-46].

Microneedles are a minimally invasive, painless and promising technology to deliver drugs into the skin barring disruption of nerve endings. This technology creates micron-sized channels in which interstitial fluid fills up the channels in the skin. It makes the hydrophilic transport pathway, allows the stratum corneum barrier, and will increase skin permeability to giant molecules [44, 46].

Vaginal delivery

In current years numerous studies show that vagina has received rich blood supply and massive surface area that means good permeability and can be a practicable route for systemic delivery to a broad range of compounds. The essential benefits of vaginal drug routes are avoidance of the first-pass metabolism, ease of administration, and exact permeability for low molecular weight drugs. For systemic delivery bile salts, dihydro fusidate, cyclodextrins, surfactants, and chelating agents have been examined as enhancers to facilitate the rate of vaginal absorption however sometimes; they caused several local reactions [44, 46].

Rectal delivery

Rectal route of delivery has been examined quickly after the discovery of insulin however, several investigators have met absorption problems via the mucosa. This administration's promising benefit is the opportunity of avoiding, to some extent, the hepatic first-pass metabolism. Absorption promoters and surfactants had been used to furnish the highest hypoglycemic effect in rectal insulin delivery. The most effective rectal absorption enhancer polyoxyethylene-9-lauryl ether (POELE) or sodium salicylate, was once used in insulin suppositories on diabetic dogs. It was once investigated that the hypoglycemic effect can be achieved via about 50-55 % [47].

Insulin devices using pen devices

It is a convenient and correct technique for insulin delivery. It intends to enhance glycemic control by making it much less difficult to comply with the present-day recommendations for intensive insulin regimens. Two sorts of pens are available; prefilled and reusable. Pens are available in various styles. Insulin pens have the potential to become an essential asset for elevated compliance amongst all patients undergoing insulin therapy.

Other novel strategies in insulin delivery

Erythrocytes, which are the most abundant cells in the body, can be used as tremendous carriers of many different drugs together with insulin. Biocompatibility, biodegradability, long circulation half-life, and the potential to get loaded with a variety of chemically and biologically active compounds make resealed erythrocytes outstanding carriers of therapeutic agents [48]. Dendrimers are macromolecules with highly branched 3D structures [49]. They additionally are used for the successful delivery of insulin.

CONCLUSION

The research and developments in insulin delivery are really promising. Many problems make the patient hesitant to provoke insulin therapy. So, many alternative routes for insulin delivery are beneath research and some of them are available. Each one has its benefits as well as drawbacks. An appropriate alternative, with high effectivity and good patient compliance, is probably to emerge in the

future to help out people with type1 diabetes, gestational diabetes, and type 2 diabetes not managed with oral hypoglycaemic agents.

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All the authors have contributed equally.

CONFLICTS OF INTERESTS

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