Various Emerging Trends in Insulin Drug Delivery Systems

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Authors’ contributions

This work was carried out in collaboration between all authors. Author TM designed the study, Authors Y and SB wrote the protocol, and wrote the first draft of the manuscript. Authors Md. Z and TM managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI:10.9734/BJPR/2015/12528
Editor(s):
(1) Rafik Karaman, Bioorganic Chemistry, College of Pharmacy, Al-Quds University, USA.
(2) Alyautdin Renad N, The Department of Pharmacology, I. M. Sechenov MSMU, Russia.

Reviewers:
(1) Anonymous, Italy.
(2) Anonymous, Spain.
(3) Anonymous, Norway.
(4) Wei Wu, School of Pharmacy, Fudan University, China.
(5) Anonymous, Malaysia.
(6) Anastasia Thanopoulou, Diabetes Centre and Department of Internal Medicine, National University of Athens, Hippokration General Hospital, Athens, Greece.

Complete Peer review History: http://www.sciencedomain.org/review-history.php?id=833&dt=14&aid=7718

Received 4th July 2014
Accepted 28th November 2014
Published 9th January 2015

ABSTRACT

Lowering of blood glucose level in patients can be achieved by insulin therapy as it plays a key role in the control of hyperglycaemia for type 1 diabetes. Insulin delivery systems that are currently available include syringes, infusion pumps, jet injectors and pens. The tedious part for the type 1 diabetes patients is to tolerate needle after needle injections while undergoing treatment for both glucose measurement and to deliver insulin. A rigorous research effort has been undertaken worldwide to replace the authentic subcutaneous route by a more accurate and non-invasive route. The newer methods explored include the artificial pancreas with closed-loop system, transdermal insulin, and buccal, oral, pulmonary, nasal, ocular and rectal routes. The future trends include use of insulin inhalers, transdermal patches, pills, pumps etc. Some of the non-invasive delivery systems include polymeric hydrogels and insulin loaded bioadhesive poly (D,L-lactide-co-glycolide)

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nanoparticles for oral delivery, aerosolized liposomes with dipalmitoyl phosphatidylcholine for pulmonary delivery, β cyclodextrins for nasal delivery, microneedle arrays fabricated from hyaluronic acid and iontophoresis for transdermal delivery, chitosan-zinc-insulin complex for the controlled delivery of insulin.

Keywords: Insulin; diabetes; drug delivery methods; non-invasive drug delivery systems.

1. INTRODUCTION

Insulin therapy is used for treatment of diabetes, it controls hyperglycaemia in type 1 diabetes patients while in patients with type 2 diabetes it may be required in selective individuals or in later stages. Insulin was clinically used first in 1922 and was isolated in 1921 [1]. The major advances achieved in this area include the synthesis of human insulin analogues by recombinant technology. Insulin syringes, insulin infusion pumps, jet injectors and pens are the currently available methods for insulin delivery. Subcutaneous injection is the traditional method for the administration of insulin. Elimination of the need to deliver insulin exogenously and regain the ability of patients to produce and use their own insulin are the ultimate goals.

Major drawback of current forms of insulin therapy is its invasive nature. Good glycaemic control in type 1 diabetes is achieved with three or more daily insulin injections. In order to decrease the suffering and improve the adherence in insulin regimens, non-invasive approaches for insulin delivery are being pursued along with the use of supersonic injectors, infusion pumps, sharp needles and pens. Ability to elicit effective and predictable lowering of blood glucose level and minimizing the risk of diabetic complications determines the success of the route of administration. Artificial pancreas with closed-loop system, transdermal insulin, and buccal, oral, pulmonary, nasal, ocular and rectal routes are the newer methods explored [2].

2. MODERN INSULIN DELIVERY SYSTEMS

2.1 Insulin Pen Injectors

These are the one of major advances in the insulin delivery that has made self-injection easier and convenient. These are smaller devices that consist of syringe and insulin cartridge and make use of smaller gauge needles that may result in less painful injections [3]. There are two pen systems: durable and prefilled. A durable pen uses a replaceable insulin cartridge. A prefilled pen is entirely disposable. Fig. 1 shows types of prefilled insulin syringes [4]. Insulin pens have a number of advantages: it is more convenient and easier to transport than traditional vial and syringe and repeatedly more accurate dosages can be obtained through it. The disadvantage of insulin pen is that unlike with the traditional syringe, two different insulins cannot be mixed by the user in an insulin pen [5].

![Fig. 1. Two types of modern prefilled insulin syringes](image)

2.2 External Insulin Pumps

External insulin pumps are small devices the size of a pager that can be attached to your belt or placed in your 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 your abdomen [6]. The working of an insulin pump is shown in Fig 2 [7]. 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 levels are high. The main advantage of pump is that it closely mimics the slow but continual release of insulin by the pancreas. The drawback is the risk of episodes of low blood sugar (hypoglycaemia) is higher and there is also the risk of ketoacidosis if the catheter blocks [6,8].
2.3 Implantable Insulin Pumps

An implantable insulin pump is implanted just under the skin (usually in the abdominal area) it works as an external insulin pump. Insulin is delivered into the peritoneal cavity and not into the subcutaneous tissue, refilling should be with special, highly concentrated insulin every 2 to 3 months depending on the insulin requirements of the patient [3].

2.4 Transfersome

Transfersome means “carrying body”. A Transfersome carrier is an artificial vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and, potentially, targeted drug delivery. The carrier aggregate consists of at least one amphiphat (such as phosphatidylcholine), which in, aqueous solvents self-assembles into a lipid bilayer that closes into a simple lipid vesicle. By addition of at least one bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) lipid bilayer flexibility and permeability are greatly increased [9]. Transfersomes can be prepared by (a) thin film hydration technique and (b) modified hand shaking, lipid film hydration technique. Transfersomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transfersomes are more elastic than the standard liposomes and thus well suited for the skin penetration [10]. The application of insulin-laden transfersomes over 40 cm² would provide the daily basal insulin needs of a typical patient with type 1 diabetes. Transfersomes mediated drug delivery through the skin is little affected by molecular size of carrier associated over the ingredient [3]. Systemic normoglycaemia that lasts at least 16 hours has been achieved using a single non-invasive, epicutaneous administration of insulin in Transfersomes [11]. Transfersomes are chemically unstable because of their predisposition to oxidative degradation lack of purity of the natural phospholipids comes in the way of adoption of transfersomes as drug delivery vehicles and transfersomes formulations are expensive to prepare [12].

2.5 Insulin Inhalers

Inhalable insulin is not a modern method of insulin delivery as it was withdrawn from the market in October 2007 due to concerns of lung cancer. However, it has been included here only for lesson. However, a new inhalable insulin product was approved for sale in the United States by the FDA in June of 2014, and hence may become available [13].

Non-invasive, well-tolerated with potential for both type 1 and 2 diabetes are advantages of inhaled insulin [14]. Comparable results for glycemic control for inhaled insulin with subcutaneous insulin were indicated in short term studies [15]. A type of insulin inhaler is shown in Fig. 3. As compared to conventional subcutaneous insulin, rapid and sustainable patient satisfaction and a positive impact on psychological well-being in patients with type 1 diabetes was obtained with inhaled insulin [16]. Patient satisfaction, quality of life and acceptance of intensive insulin therapy are the advantages of inhaled insulin [17]. The pharmacokinetic profile of inhaled insulin has both advantages and disadvantages compared with subcutaneous insulin injection. Because inhaled insulin is more quickly absorbed, pulmonary insulin delivery may reduce the time necessary between insulin administration and mealtimes. However, because the duration of action of inhaled regular insulin is short, a once-daily injection of long-acting insulin should be administered to patients who previously required multiple insulin injections daily. The bioavailability of inhaled insulin is less than 20%; thus, dosage requirements and cost per treatment are increased in comparison with insulin administered by subcutaneous injection [18].
Patients receiving inhaled insulin had more episodes of hypoglycemia and gained more weight than did patients treated with oral agents [19,20]. Mild to moderate cough was also reported in up to 25% of patients receiving inhaled insulin [21-23]. Uncontrollable factors also affect pulmonary absorption, and smokers need lower [24] and asthmatics higher doses [25]. The pulmonary insulin dose required for a similar glycemic effect is approximately 20 times that required for a subcutaneous injection [26], and insulin directed antibodies are an issue [27,28].

![Insulin inhaler](image)

**Fig. 3. Insulin inhaler**

### 2.6 Insulin Spray

Another promising alternative for insulin delivery is the buccal route. Delivery of the acid labile insulin, and elimination of insulin destruction by first pass metabolism are the advantages of buccal area as it has an abundant blood supply. The patient does not inhale with the buccal spray device as the formulation is delivered as fine spray onto the buccal mucosa as shown in the Fig. 4. Rapid absorption into the bloodstream is allowed with high-speed spray. Inhaled insulin formulation shows the risks to lung tissue, this can be avoided as the drug gets deposited onto the buccal mucosa [29-34].

![Insulin spray](image)

**Fig. 4. Insulin spray**

Azopolymer coated pellets entrap therapeutic agent till the pellets reach the colon and hence used for delivering the insulin to the colon region. The bacteria inhabiting the colon, secrete enzymes which can breakdown the azopolymer, this initiates the release of insulin from pellets [39]. Insulin is microencapsulated using pH responsive polymers. Alginate is one such polymer, its coating protects them in the acidic pH of the stomach but dissolves and liberates the entrapped insulin in the intestine [40]. Pilot trials are being conducted to develop insulin pills which may prove to be a potential alternative to injected or pumped insulin. Novel delivery technology is required for this attempt [30,41,42].

### 2.7 Insulin Pill

Controlling postprandial glycaemia requires several daily injections of insulin. Treatment using insulin through subcutaneous or other parenteral route results in peripheral hyperinsulinema, this may also include coronary artery disease, hypertension, dyslipidemia and weight gain along with the risk of hypoglycaemia. An oral insulin product have proved to adequately insulinize the liver as it provides insulin in more physiological manner, with a resultant decrease in peripheral insulin [30,35,36]. Researchers have found that insulin can be protected in a chemical coating known as a novel polymer, bringing the chance of oral insulin, an insulin capsule, ever closer. The coating is a key step to ensure that insulin taken in pill form is not broken down by enzymes and rendered useless before entering the blood stream [37,38].

![Insulin Pill](image)

**Azopolymer coated pellets entrap therapeutic agent till the pellets reach the colon and hence used for delivering the insulin to the colon region.**

### 2.8 Transdermal Patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin into the bloodstream [43]. The Altea Therapeutics Pass Port™ System was the first product to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. It consists of an applicator and a reservoir patch as shown in the Fig. 5; the latter is placed on the skin and provides for painless delivery of insulin. It enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications. It also avoids the first-pass gastrointestinal and liver metabolism that occurs often.
after oral administration. It creates an effective economical and patient-friendly delivery of insulin as well as the delivery of drugs for a wide variety of conditions [30,44].

However the transdermal patch system has its own limitations in which the drug that require high blood levels cannot be administered and may even cause irritation or sensitization of the skin. The adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product [45].

Fig. 5. The passport™ system applicator (on the left) and reservoir patch

2.9 Iontophoresis

It refers to transdermal delivery of insulin or other peptides by direct electric current. A weak current carries drug ions through the skin to cause vasodilation and increased blood perfusion. Fig. 6 shows an iontophoresis patch used for the transdermal delivery [46]. Iontophoresis differs from transdermal medication patch by using a low-level electrical current in the process, enhancing the delivery of drug ions into the skin and surrounding tissues. Depending on the net charge of the insulin molecule, the applied electrical potential has been shown to increase the rate of insulin transfer across skin [47]. It offers the option of a programmed drug delivery technique that physically facilitates the transport of permeates across the skin [48]. Gels are considered the most suitable delivery vehicle for iontophoresis, because they can easily be amalgamated with the iontophoretic delivery system and match the contours of the skin [49].

Fig. 6. Iontophoresis patch

2.10 Islet Cell Transplant

Constant normoglycaemic state and avoiding hypoglycaemic episodes can be achieved by islet transplantation which is far superior compared to conventional insulin treatment. Insulin-producing beta cells are taken from a donor's pancreas and transferred into a person with diabetes. Once transplanted, the donor islets begin to make and release insulin, actively regulating the level of glucose in the blood [50]. Fig. 7 depicts the process of islet cell transplantation for the treatment of diabetes mellitus [51]. Procedure for islet transplantation involves enzymatic digestion of the pancreatic tissue, purification of the islets from exocrine tissue infusion of the islets into the portal vein and implantation in the liver [52]. The percutaneous trans hepatic approach for the implantation of islet cells into the portal vein is a safe procedure [53]. Successful transplantation can provide the following benefits:

1. Need for daily insulin injections and frequent blood glucose measurements are eliminated
2. Flexibility with meal planning
3. Provides protection against heart disease, kidney disease, stroke and nerve and eye damage which are the long-term complications of diabetes [30,54].

Fig. 7 depicts the process of islet cell transplantation for the treatment of diabetes mellitus [51]. Procedure for islet transplantation in involves enzymatic digestion of the pancreatic tissue, purification of the islets from exocrine tissue, infusion of the islets into the portal vein and implantation in the liver [52]. The percutaneous trans hepatic approach for the implantation of islet cells into the portal vein is a safe procedure [53]. Successful transplantation can provide the following benefits:

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2.11 Gene Therapy

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. Fig. 8 illustrates gene therapy using an adenovirus vector. A new gene is inserted into a cell using an adenovirus. If the treatment is successful, the new gene will make functional protein to treat a disease [55]. To regulate insulin a gene called SHIP2 has been identified which provides a potential gene therapy target for the treatment of type 2 diabetes [56]. The first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID [57]. Since then, over
1,700 clinical trials have been conducted using a number of techniques for gene therapy [58].

### 2.12 Insulin Analogues

An insulin analogue is an altered form of insulin, available to the human body to control the glucose levels same as insulin. To alter its ADME (absorption, distribution, metabolism, and excretion) characteristics the amino acid sequence of insulin can be changed by genetic engineering of the underlying DNA to produce insulin analogues [59]. Table 1 shows different insulin analogues and their duration of action. Analogue insulin is available in two main forms, rapid acting and long acting, as well as premixed combinations [60].

#### 2.12.1 Rapid-acting insulin analogue

They are the fastest-working insulins. Rapid-acting insulin analogues include: Aspart, Glulisine, Lyspro. As they enter the bloodstream within minutes, it is important to inject them within 5 to 10 minutes of eating. They have a peak action period of 60-120 minutes, and fade completely after about four hours.

#### 2.12.2 Long-acting injected insulin analogue

Long-acting insulin works for the longest period of time and provide relatively constant insulin levels that plateau for many hours after injection. They are also called as “peakless” insulins. They have an onset of action within 60-90 minutes, maximum effect in around 5 hours that gradually wanes over the next 12-24 hours. They include: Insulin detemir (Levemir®), Insulin glargine (Lantus®) [61]. NPH (Neutral Protamine Hagedom) insulin may need to be administered up to three times daily in type 1 patients to provide sufficient insulin supply throughout the day as its duration of action is 14 h and plasma insulin peak level is achieved 4-6 h after administration [62].

#### 2.12.3 Premixed analogue

Premixed analogue insulins combine a ratio of rapid acting and long acting insulin. For example, Humalog Mix 25 consists of 25% rapid acting and 75% long acting insulin.

The rapid acting insulin works as soon as it is injected and long acting insulins have no peak activity, these are the primary benefits of analogue insulin. Rapid acting insulin minimise sharp rises (spikes) in blood sugar shortly after eating and hence useful for insulin dependent patients. The lack of a peak activity period gives some people more confidence that they will avoid night time hypos, this made long acting analogue insulins quite popular.

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**Fig. 7. Process of islet transplantation**
Table 1. Insulin and insulin analogues

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of action (minutes)</th>
<th>Time to peak concentration (minutes)</th>
<th>Maximum duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular insulin</td>
<td>30-60</td>
<td>90-120</td>
<td>5-12</td>
</tr>
<tr>
<td>Insulin lispro (Humalog)</td>
<td>10-15</td>
<td>30-60</td>
<td>3-4</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10-15</td>
<td>40-50</td>
<td>3-4</td>
</tr>
<tr>
<td>Insulin glusine</td>
<td>10-15</td>
<td>55</td>
<td>3-5</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>60-120</td>
<td>240-480</td>
<td>10-20</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>60-120</td>
<td>None</td>
<td>24</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>60-120</td>
<td>None</td>
<td>20</td>
</tr>
</tbody>
</table>

Loss of hypo awareness, lethargy and weight gain are the side effects of analogue insulins, animal insulins lack such side effects [60].

2.12.4 Newer injectable insulins

2.11.4.1 Insulin degludec

Insulin degludec is a novel ultra-long acting basal insulin which is similar to human insulin in structure except for the last aminoacid deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadecandioic fatty acid [63]. Ultra-long action profile with half life more than 24 h can be achieved by subcutaneous injection which transforms insulin into soluble multihexamers.

2.11.4.2 VIAject™

VIAject is faster than that of human soluble insulin and insulin lispro. It is a recombinant human insulin with ultra fast onset of action. [64,65].

3. NON-INVASIVE INSULIN DRUG DELIVERY SYSTEMS

3.1 Insulin-loaded Bioadhesive PLGA Nanoparticles for Oral Drug Delivery

Poly (D, L-lactide-co-glycolide) nanoparticles (PLGA-NP) have been extensively used as a drug delivery system for proteins and peptides. CS-PLGA-NP was prepared using a water-in-oil-in-water solvent evaporation technique. Chitosan PLGA nanoparticle has attractive properties, such as a positive charge, mucosal adhesion, and absorption promotion, which prolong the duration of residence of insulin in vitro and improve its bioavailability in vivo for oral delivery. The toxicity of nanoparticle drug delivery systems has been a prominent concern. Related studies have shown that nanoparticles enhance
therapeutic effects but can also increase toxicity. But the positive properties of CS-PLGA-NP do not increase the cytotoxicity because chitosan is biocompatible, biodegradable, and has low cell toxicity. This is why it has been widely applied in tissue engineering, gene therapy, drug delivery, and other fields [66].

In another study, insulin was encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) by using double-emulsion/solvent evaporation technique and analyses on its release kinetics were carried out using both in vitro and in vivo methods. Blood glucose decreased and the concentration of insulin in animal blood increased. The experimental results indicated that oral insulin-loaded poly (lactic-co-glycolic acid) nanoparticles are able to deliver insulin effectively and decrease animal blood sugar. In conclusion, this may be a promising delivery system for the treatment of diabetes [67].

### 3.2 Polymeric Hydrogels for Oral Insulin Delivery

Hydrogels are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their three-dimensional structure. For oral delivery of proteins and peptides complexation hydrogels are suitable due to their ability to respond to changes in pH in the GI tract and provide protection to the drugs from the harsh environment of the GI tract [68]. Polymeric hydrogels protect insulin from enzymatic degradation in acidic stomach and delivers effectively in the intestine. Swelling and deswelling mechanisms of the hydrogel under varying pH conditions of the body control the release of insulin. Combining enzyme inhibitors within polymeric systems represents the potential to increase the potency of orally administered insulin. Several insulin derivatives with increased physicochemical and biological stability such as alkylated / acylated insulin, PEGylated and polysialylated insulins have been the most promising candidates for oral administration [69].

In a study, Polyelectrolyte crosslinked hydrogel was synthesized using gamma radiation-induced copolymerization of methacrylic acid (MAA), N,N-dimethyl aminoethyl methacrylate (DMAEMA) in aqueous solution to utilize for oral delivery of insulin. Drug release studies showed that the increasing content of MAA in the copolymer enhances release in simulated intestinal fluid to design and improve insulin release behavior from these carriers [70].

In another study, cationic hydrogel sub-microparticles based on poly dimethyl amino ethyl methacrylate for oral insulin delivery were synthesized and evaluated in vitro. Polymerization of dimethyl amino ethyl methacrylate was carried out in aqueous medium with potassium persulfate as the initiator. cationic surface groups were introduced by the quaternization of the resulting hydrogel and the derivatization was confirmed by zeta potential measurements, nuclear magnetic resonance and infrared spectroscopies. Insulin-loaded particles were subjected to in vitro release experiments at gastric and intestinal pH [71].

### 3.3 Acrylic Polymers for Oral Insulin Delivery

Acrylic polymers are synthetic mucoadhesive polymers, principally used for oral drug delivery. Synthetic polymers can be generated by diverse techniques such as nanoprecipitation, solvent evaporation, freeze–drying or spray drying of emulsions and supercritical fluid technology [72]. The efforts to develop an oral insulin nanotechnology delivery system started in the late 1980s with poly alkylcyano acrylate nanocapsules, for which a remarkable hypoglycemic effect has been reported [73]. Recent studies have demonstrated the potential of poly alkyl cyano acrylate (PACA) as a colloidal carrier of drugs. PACA not only enhances the oral absorption of insulin but also prolongs its action in the presence of protease inhibitors. Capric acid & glycyrrhizic can be used as oral absorption enhancers [74]. pH-sensitive copolymeric hydrogels prepared from N-vinylcaprolactam and methacrylic acid monomers by free radical polymerization offered 52% encapsulation efficiency and evaluated for oral delivery of human insulin. The formulations of this study are the promising carriers for oral delivery of insulin [75].

Nanospheres of crosslinked networks of methacrylic acid grafted with poly (ethylene glycol), and acrylic acid grafted with poly (ethylene glycol) nanospheres for use as oral insulin delivery devices were developed. Free-radical precipitation/dispersion was used for the synthesis of copolymer nanospheres. By partitioning from concentrated insulin solution, insulin was loaded into the copolymers at levels of 9.33 and 9.54 mg per 140 mg solid sample. In vitro studies were performed to study the passage of the insulin-loaded copolymer
samples in the gastrointestinal tract. In studies with diabetic rats, the serum glucose level was lower for the animals that received the insulin-loaded copolymers than control values and lasted for at least 6 h. The insulin loaded copolymer nanospheres caused a significant reduction of serum glucose with respect to that of a control animal [76].

3.4 Aerosolized Liposomes for Pulmonary Delivery of Insulin

Pulmonary route for systemic delivery of therapeutic agents (mainly peptides and proteins) is paid more attention because its a non-invasive method of administration and hence valuable for the delivery of large molecular proteins. The lungs provide good blood supply, a large absorptive surface area with extremely thin absorptive mucosal membrane. The anatomic structure of the human respiratory system and the effect of disposition exerted by the respiration process makes the pulmonary delivery of peptides and proteins is complicated [77]. Aerosolized liposomes with phosphatidylcholine enhance pulmonary insulin delivery by opening the epithelial cells space in pulmonary mucosa and not mucosal cell damages and, also, a smaller liposomal particle size is advantageous for enhanced pulmonary delivery [78].

3.5 β-Cyclodextrin Grafting Hyperbranched Polyglycerols as Carriers for Nasal Insulin Delivery

Insulin-loaded HPG-g-CD nanoparticles had the ability to significantly decrease the blood glucose concentrations. CDs are believed to enhance nasal absorption of peptides and proteins by inhibiting their enzymatic degradation, disrupting the epithelial membrane by extraction of phospholipids and proteins, and/or opening tight junctions and the positive charge of the nanoparticles might also play an important role, since the interaction of positively charged material with the negatively charged epithelium would be helpful for opening the tight junction and facilitating the absorption of drugs across the paracellular pathway [79].

3.6 Chitosan–zinc–insulin Complex Incorporated Thermosensitive Polymer for Controlled Delivery of Basal Insulin

Nanoparticles composed of naturally occurring biodegradable polymers have emerged as potential carriers of various therapeutic agents for controlled drug delivery through the oral route. Chitosan, a biodegradable polymer and a cationic polysaccharide, has been extensively exploited for the preparation of nanoparticles for oral controlled delivery of many pharmacologically active agents [80]. Chitosan derivatized polymers that improve drug retention capability, provide improved permeation, enhanced mucoadhesion and sustained release of therapeutic agents are more important [81,82]. Thermosensitive polymeric delivery system (PLA-PEG-PLA) loaded chitosan–zinc–insulin complex was designed for continuous in vivo insulin delivery at basal level for prolonged period after a single subcutaneous injection. Chitosan–zinc–insulin complex was optimized to restrict the diffusion of insulin from the delivery system by forming large complexes and thereby reducing the initial burst release. The insulin released from the delivery systems did not provoke any immune response. The delivery systems demonstrated excellent biocompatibility both in vitro and in vivo and were non-toxic. In vitro release studies indicated that the increased size of chitosan–zinc–insulin complex helped to reduce complex diffusion from the thermosensitive polymer gel matrix, and prolonged the insulin release in vitro. This slow diffusion of insulin resulted in reduced initial burst release, stabilize insulin during release and storage, while providing controlled release over extended duration in vitro. The polymeric delivery system containing chitosan was biodegradable, biocompatible in vivo. This signifies that the chitosan–zinc–insulin complex incorporated in the thermosensitive polymeric delivery system can be used as an alternative to the conventional daily multiple dose basal insulin therapy [83].

3.7 Semi-interpenetrating Network (sIPN) Co-electrospun Gelatin/insulin Fiber Formulation for Transbuccal Insulin Delivery

Insulin can be fabricated into a semi-interpenetrating network co-electrospun gelatin/insulin fiber (sIPN-GIF) formulation following co-electrospinning and cross-linking without losing bioactivity. Gelatin was electrospun into fibers and converted into a sIPN following eosin Y-initiated polymerization of polyethylene glycol diacrylate (PEG-DA). Insulin was co-electrospun with gelatin into fibers and converted into a sIPN-GIF using this suitable formulation. ELISA was used for the in vitro release kinetics of insulin. In vitro porcine oral mucosa model was used to determine the transbuccal permeability of released insulin. Degradation half-life of 49 min
which is a moderate degradation rate, significant enhancement in mechanical properties and no cytotoxic effects were found in the sIPN-GF formulation of GF cross-linked by PEG-DA (1% w/v) with eosin Y (5% v/v). Insulin release was extended up to 4 h by using This formulation to fabricate sIPN-GIF. Intracellular AKT phosphorylation and induced adipocyte differentiation in 3T3-L1 preadipocytes were successfully started by the released insulin [84-86].

3.8 Films Loaded With Insulin-coated Nanoparticles (ICNP) as Potential Platforms for Peptide Buccal Delivery

Insulin-coated nanoparticles (ICNPs) can be obtained by a new antisolvent co-precipitation fabrication process. The ICNPs were embedded in polymeric films containing a cationic polymethacrylate derivative (ERL) or a combination of ERL with hydroxypropyl methylcellulose (HPMC). ICNPs with 40% (w/w) insulin load was successfully obtained by the antisolvent co-precipitation method, 323±8 nm particles with a high zeta potential of 32.4±0.8 mV, indicating good stability were achieved. One month storage did not decrease the insulin content. ICNP-embedded films using ERL as the polymer matrix presented excellent mucoadhesive and insulin release properties. ICNP-loaded ERL formulations are a promising delivery system for buccal administration of a peptide such as insulin, as they were found to be more effective in terms of film performance and insulin permeation through the human buccal mucosa model [87,88].

4. INVASIVE INSULIN DRUG DELIVERY SYSTEMS

4.1 Novel Microneedle Arrays Fabricated from Hyaluronic Acid for the Transdermal Delivery of Insulin

Microneedles have been regarded as a potential technology to be employed alone or with other enhancing methods such as electroporation and iontophoresis, and with different drug carriers (e.g., lipid vesicles, micro- and nanoparticles) [89,90]. Microneedles are a promising technology to deliver drugs into the skin, as microneedles inserted into the skin of human subjects are reported to be painless [91].

Microdermabrasion can increase skin permeability to insulin at levels sufficient to reduce blood glucose level [92]. Microneedle arrays uses a system to push the drugs through tiny needles, which do not go far enough under the skin to trigger pain receptors as shown in Fig. 9 [93]. Microneedle technology involves the creation of micron-sized channels in the skin, thereby disrupting the stratum corneum barrier. Upon creation of the microchannels, interstitial fluid fills up the channels, resulting in hydrophilic pathways. It offers a cost-effective, minimally invasive, and controllable approach to transdermal drug delivery [94]. Delivering insulin into the systemic circulation via the skin by the use of the novel insulin-loaded micro needles using hyaluronic acid for fabrication is an alternative form that does not induce any skin damage. Complete absorption of insulin from the skin into the systemic circulation when administered using microneedles was proved from the Pharmacodynamic and pharmacokinetic data. The hypoglycemic effect is almost same for insulin-loaded microneedles and subcutaneous injection of insulin. Hygroscopy, stability, drug releasing profiles, and dissolution properties are the important characteristics of insulin-loaded hyaluronic acid microneedles [95].

4.2 Transdermal Delivery of Insulin by Amided Pectin Hydrogel Matrix Patch

The application of pectin insulin (PI)-containing dermal patches of different insulin concentrations sustain controlled release of insulin into the bloodstream of streptozotocin (STZ)-induced diabetic rats with concomitant alleviation of diabetic symptoms in target tissues, most importantly, muscle and liver. PI dermal matrix patches were prepared by dissolving pectin/insulin in deionised water and solidified with CaCl2. Oral glucose test responses of diabetic rats exhibited lower blood glucose levels. The control non-diabetic rats showed higher plasma insulin concentrations than the untreated diabetic rats [96].

4.3 Dissolving Polymer microneedle Patches for Rapid and Efficient Transdermal Delivery of Insulin

For the rapid and efficient transdermal delivery of insulin, dissolving microneedle patch composed of starch and gelatin was used. The microneedles completely dissolve after insertion into the skin for 5 min, quickly releasing their encapsulated payload into the skin. Hypoglycemic effect in rats receiving insulin
loaded microneedles and a subcutaneous injection of insulin was found to be similar. Pharmacological activity is retained even after encapsulation of insulin, as both the relative pharmacological availability and relative bioavailability of insulin were approximately 92%. The microneedles retain 90% of insulin even after one month of storage 25 or 37°C. Stable encapsulation of bioactive molecules by using starch/gelatin is confirmed from the results and hence relatively painless, rapid, and convenient method for transdermal delivery of protein drugs [97].

5. CONCLUSION

The long term complications of diabetes mellitus can be reduced by the advanced methods of insulin delivery systems. Effort has been undertaken to replace the invasive subcutaneous route by a non-invasive route. There has been a significant progress in the delivery of insulin via pulmonary, buccal and oral route. Each route has their own set of advantages and disadvantages. Of all the non-invasive methods, oral route seems to be the most promising as nanotechnology allows the various encapsulations to pass through the gastric acid environment. Oral route also provides improved absorption rates and ease of administration and thus, improves patient compliance. Of the various emerging trends, artificial pancreas may prove to be a valuable therapy for the patients of type 1 diabetes, particularly if the lag period is shortened through improved glucose sensors and the use of ultra-fast acting insulin.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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