

# Insulin

Subjects: Pharmacology & Pharmacy

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Insulin is used for the treatment of diabetes mellitus, which is characterized by hyperglycemia. Subcutaneous injections are the standard mode of delivery for insulin therapy; however, this procedure is very often invasive, which hinders patient compliance, particularly for individuals requiring insulin doses four times a day. Furthermore, cases have been reported of sudden hypoglycemia occurrences following multidose insulin injections. Such an invasive and intensive approach motivates the quest for alternative, more user-friendly insulin administration approaches. For example, transdermal delivery has numerous advantages, such as prolonged drug release, low variability in the drug plasma level, and improved patient compliance.

Keywords: Insulin ; Skin Route ; Diabetes Mellitus

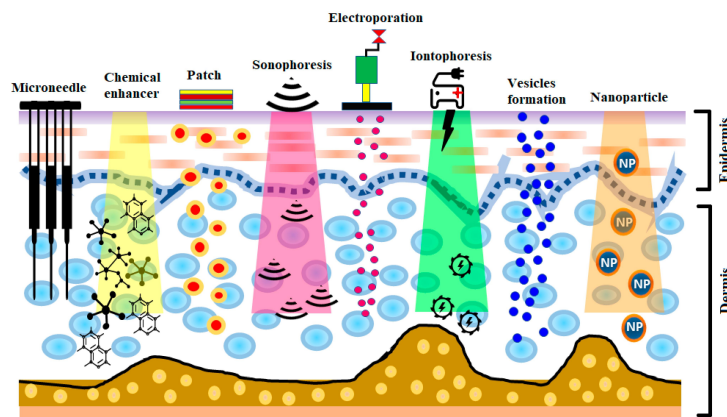
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## 1. Introduction

In the last few decades, diabetes mellitus has emerged universally as an epidemic, and has become the fifth most prominent cause of mortality <sup>[1]</sup>.

More than 422 million individuals worldwide have diabetes, according to a WHO report (see: [https://www.who.int/health-topics/diabetes#tab=tab\\_1](https://www.who.int/health-topics/diabetes#tab=tab_1)). This number could increase to 693 million by 2045 if proper actions are not taken <sup>[2][3]</sup>. In general, there are two classes of diabetes mellitus, i.e., type 1 and type 2. Type 1 is mostly due to a total insulin deficiency, but the causes of type 2 are varying degrees of insulin resistance, impaired insulin secretion, and elevated glucose production. Type 1 may be further subcategorized into type 1A diabetes mellitus, i.e., the autoimmune degradation of  $\beta$ -cells, and type 1B, i.e., idiopathic insulin deficiency <sup>[4]</sup>. The incidence of diabetes is growing owing to an aging population and improved diagnosis <sup>[5][6]</sup>.

The development of insulin has been identified as one of the most significant events in the treatment of diabetes. The production of human insulin analogs using recombinant technology was seen as a huge step forward <sup>[7]</sup>. Insulin therapy has a significant role in treating type 1 diabetes. The subcutaneous route has been the most widely used, as it precludes enzymatic insulin degradation in the digestive tract. Healthy glycemic controls need to be preserved in type 1 diabetes, requiring at least three or maybe more daily insulin shots. Nevertheless, this route comes with the risk of infection and inflammation induced by the use of subcutaneous needles. Later, alternative routes—for instance, pulmonary, nasal, and oral routes—were investigated <sup>[8][9]</sup>. Pens, jet injectors, sharp needles, supersonic injectors, and infusion pumps have been introduced to minimize pain and enhance adherence to insulin regimens <sup>[10][11][12][13]</sup>. Still, compared to subcutaneous injections, the insulin absorption from the aforementioned techniques into the blood is quite low, and, consequently, other systems for insulin therapy are required <sup>[14][15]</sup>. Some noninvasive methods are being explored for insulin delivery <sup>[14]</sup>. Recently, there has been significant interest in the delivery of drugs via the transdermal route <sup>[16]</sup>. The transdermal route is an interesting choice for insulin delivery, as this approach would mitigate the pain and infection risk related to subcutaneous injections <sup>[17]</sup>. Furthermore, the transdermal route ensure patient compliance as well as delivery-controlled insulin release over time <sup>[18][19]</sup>. Still, the transdermal delivery of drugs is restricted, owing to the low permeability of the stratum corneum <sup>[20][21][22][23][24]</sup>. In recent years, a number of experimental techniques seeking to improve transdermal insulin delivery have been proposed <sup>[18][25][26][27][28][29][30]</sup>. In this review, different transdermal insulin delivery techniques and their improvements for diabetes care are highlighted. A schematic illustration of various strategies for insulin delivery via the transdermal route is presented in Figure 1.

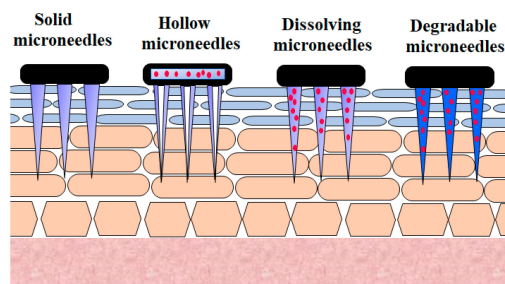


**Figure 1.** A schematic illustration of various strategies for insulin delivery via the transdermal route.

## 2. Delivery of Insulin via Skin Route

### 2.1. Microneedle

Microneedle technology offers an appealing technique for generating reversible skin microchannels that improves the skin permeability and allows the delivery of a wide variety of biotherapeutics, including insulin [31]. The delivery of microneedles at the site of application causes substantially less anxiety, pain, and tissue harm, owing to their minute size, as opposed to that of the 26-G hypodermic needle [32]. Micrometer-sized needles are sufficiently long to reach the corneum [33][34][35][36]. They are adequately narrow and sharp to cause minimal trauma and decrease the probability of infection [32][37]. This method offers a similar efficiency to standard injections. Besides this, the microneedle approach reduces the inherent problems associated with other invasive techniques [38]. Various microneedles employed for the transdermal delivery of insulin are presented in Figure 2.



**Figure 2.** Various microneedles employed for transdermal insulin delivery.

### 2.2. Chemical Permeation Enhancer

The term “chemical permeation enhancer” applies to a substance or mixture of substances that enhances the permeability of the skin. Several groups of permeation enhancers have been tested for the delivery of various lipophilic and hydrophilic drugs(s) using both human and animal skins [39][40].

Transdermal enhancers (linolenic acid and oleic acid) and microwave techniques have recently been investigated to improve transdermal insulin permeation. The transdermal enhancer, linoleic acid, was the least active in terms of increasing the delivery of transdermal insulin, while the permeability enhancer, oleic acid, was found to be stronger than linolenic acid but failed to provide significant insulin permeation. The best result was found with microwave technology that facilitates insulin absorption and decreases the blood glucose levels in animals [41].

Previously, different chemical permeation enhancers were examined by Yerramsetty et al. to ameliorate skin permeability for the delivery of insulin. Amongst the investigated permeation enhancers, a total of eight, i.e., decanol, menthone, oleic acid, cycloundecanone, cis-4-hexen-1-ol, 2,4,6-collidine, octaldehyde, and 4-octanone, were found to be highly enhancing and nontoxic, five (cis-4-hexen-1-ol, 2,4,6-collidine, cycloundecanone, 4-octanone, and octaldehyde) of which were new discoveries [42].

### 2.3. Patches

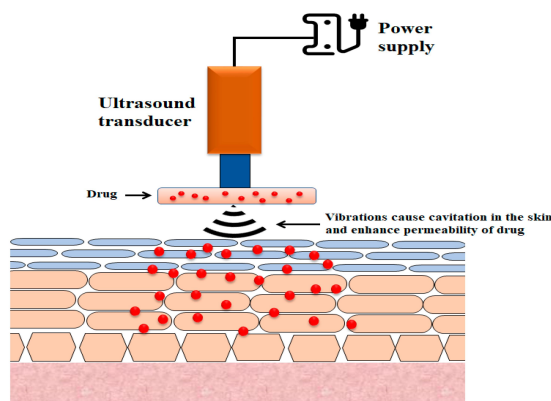
In particular, transdermal patches are an appealing dosage method for the predictable and consistent delivery of insulin into the bloodstream. Insulin patches contribute to patient-friendly, noninvasive and painless delivery of insulin. Even, in the case of hyperinsulinemia, patients can easily remove the patches. Recently, nanoheaters incorporated into insulin

patches were shown to effectively release insulin, and demonstrated comparable *in vivo* activity in mice with respect to s.c. injection of insulin [43].

In 2002, an innovative transdermal lipid-based system (Biphasix-insulin) was produced by King et al. and tested for blood glucose-reducing efficacy in a diabetic rat model induced by streptozotocin. Biphasix-insulin-containing transdermal patches (recombinant human insulin dose 10 mg) were administered to abdominal skin of rats with diabetes for 48 h. A blood glucose level decrease of 43.7%, compared to initial values, was observed. Further, the insulin bioavailability was improved by 21.5%, based on the serum insulin noted from the transdermal Biphasix-insulin patches. It was concluded that the Biphasix device successfully administered insulin via the skin route. These findings support the use of patches containing insulin for human use [29]. In 2003, King et al. reported that insulin in biphasic vesicle-containing transdermal patches had been administered to the abdominal skin of diabetic rats for 73 h, and the levels of blood glucose tested using a glucose meter every 2–10 h. ELISA was used to measure the inguinal lymph node insulin samples. The findings showed that insulin increased in the lymph nodes in a manner that depended on the dose and time. The maximum transdermal lymph node insulin concentrations were reported at 73 h with both 140 IU and 280 IU doses of recombinant insulin. The authors concluded that lymph transport is involved after transdermal insulin delivery of biphasic vesicles [44].

## 2.4. Sonophoresis

The use of ultrasound to enhance transdermal drug transport is referred to as phonophoresis or sonophoresis (Figure 3) [45]. It was observed that the increase in insulin delivery by the skin route that resulted from the use of ultrasound waves (low-frequency 20–100 kHz) could be due to the disruption of stratum corneum layers [46][47]. While sonophoresis has received considerable attention from researchers, its mechanisms are not fully understood, although several probable mechanisms have been suggested, the most plausible of which is cavitation [48][49].



**Figure 3.** Illustration of the basic design of sonophoretic delivery devices.

## 2.5. Electroporation

In this process, short, high-voltage electric field signals generate transient aqueous paths in the stratum corneum [50][51][52] [53]. Researchers showed that electroporative pulses could be used in diabetic rabbits to regulate blood sugar by improving insulin transportation through the skin. It was highlighted that the increment in insulin dose and electroporative pulses, and decrease in the field strength of electroporation, contributed to a dramatic reduction in the blood sugar levels [54]. In the original report, investigators used a combination of electroporation and iontophoresis to study insulin permeation in rats. The investigators found that the combination of these techniques led to an increase in insulin plasma levels in comparison to those reported following electroporation [55]. In another study, an *in vivo* potency of the electroporation of insulin as a solution, insulin solution (s.c.), nanoparticle (i.v.) and nanoparticles (electroporation) was discussed. These findings indicated that polymeric nanosystem electroporation was an attractive substitute to injectable administration [56]. Other research indicated that, compared to electroporation alone, electroosmosis combined with electroporation in the presence of 1,2-dimyristoylphosphatidylserine (a saturated anionic lipid) contributed a substantially higher transport rate of insulin [57].

## 2.6. Iontophoresis

One possible method for the improvement of drug delivery is transdermal iontophoresis [58][59]. Hao et al. stated that transdermal insulin delivery could potentially be achieved by combining iontophoresis and some enhancers [60]. Elsewhere, transdermal insulin delivery through porcine epidermis was observed by combining the use of iontophoresis with different chemical enhancers [61][62]. In 2002, researchers demonstrated the application of simultaneous techniques, such as iontophoresis + electroporation, for insulin permeation augmentation through human cadaver skin *ex vivo* [63].

Transdermal insulin delivery using the technique of iontophoresis was demonstrated in [26][64][65][66][67][68]. In a prior study, pretreatment (wiping) of skin using alcohol before iontophoresis was said to produce an impressive increment in insulin transdermal transport [69].

## 2.7. Vesicular Formulations

Liposomes are widely-studied nano-sized lipid vesicles that could be beneficial in the delivery of drugs via the dermal or transdermal routes. Liposomes, as drug carriers, offer many advantages that are reported elsewhere [70][71][72].

Techniques such as using combinations of two or more enhancers or the liposomal formula of insulin were investigated by Ogiso et al. The highest blood sugar lowering action that continued up to 10 h was exhibited by a transdermal system comprising liposomes insulin, d-limonene, and taurocholate. A high hypoglycemia effect was also achieved with a blend of n-octyl-beta-d-thioglucoside, cineol, and deoxycholate, or d-limonene and n-octyl-beta-d-thioglucoside. The authors clearly showed that the absorption of insulin in the stratum corneum of rat skin could be achieved under certain circumstances [73].

## 2.8. Microemulsion

Microemulsions typically droplets of less than 100 nm in size, and are thermodynamically stable clear liquids [74][75][76]. Microemulsions have been extensively studied and have gained considerable interest as vehicles of transdermal administration [77][78][79][80][81][40].

In 2013, insulin emulgel was prepared using emu oil (composed of fatty acids obtained from emu, a bird, *Dromaius Novae-Hollandiae*, native to Australia) as a permeation enhancer. The biological activity of emulgel alone and in combination with iontophoresis was tested using albino rabbits. The authors claimed that the optimized formulation [F4: emu oil (7.5% w/w) and polysorbate 80 (5.0% w/w)] showed a maximum insulin permeation flux of 4.88  $\mu\text{g}/\text{cm}^2/\text{h}$  through rat skin. A pharmacodynamic study indicated that the blood glucose level decreased from an initial value of 250 mg/dL to 185 mg/dL and the initial value to 125 mg/dL in 2 h in the group treated with insulin emulgel alone and insulin emulgel + iontophoresis respectively [45].

Transdermal microemulsions containing insulin were formulated with 10% oleic acid, 50% surfactant phase, and 2% DMSO, providing a maximum flux of 4.93  $\mu\text{g}/\text{cm}^2/\text{h}$  across goat skin. The authors concluded that there was considerable potential to use microemulsions for insulin delivery via the skin route [46].

## 2.9. Nanoparticles

Earlier, the feasibility of the use of transdermal insulin nanoparticles by means of a supercritical antisolvent micronisation procedure was investigated. The authors indicated that the supercritical antisolvent procedure provided uniform spherical insulin nanoparticles of particle sizes  $68.2 \pm 10.8$  nm. The research indicated that the supercritical antisolvent process did not cause insulin degradation. An in vitro evaluation revealed that the insulin nanoparticles followed Fick's first diffusion law, and displayed a good permeation rate. The authors found that the prepared nanoparticles containing insulin may have promising possibilities for the transdermal delivery of diabetes chemotherapy [82].

## 2.10. Microdermabrasion

Microdermabrasion has been previously used to minimize the presence of wrinkles, scars, and fine lines [83][84][85]. Previously, this approach was adopted as a tool to mitigate the hindering nature of the stratum corneum [86][87][88][89].

The application of microdermabrasion to improve skin insulin permeability was investigated by Andrews et al., who highlighted that microdermabrasion could improve the permeability of the skin to insulin at levels that are adequate to stabilize the range of blood glucose in rats with diabetes [90].

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