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A Review on Novel Routes of Insulin Administration

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A B S T R A C T

Diabetes mellitus is the chronic pathogenic condition which is primarily due to inadequate insulin secretion and is responsible for major healthcare problems worldwide cost billions of dollars annually. For more than 84 years of time, Insulin replacement therapy had been used to manage to overcome the complications and this present review is based on the various routes of insulin delivery based on its safety and efficacy. Depending upon the effective duration of action, insulin activity varies from 1.5 to 27 hours and to reduce insulin burden, now a days it can be delivered in sensor-augmented pump therapy, various types of insulin Pen as well as routes like inhalation, colonic insulin, buccal, intra- peritonea and ocular, rectal, vaginal delivery of insulin etc. had been added to it. This review examines some of the recent proposals for various routes of application of Insulin delivery system along with the particular attention to its latest intervention of novel drug delivery system.

Keywords:Diabetes Mellitus, Route Of Drug Administration, Insulin Delivery.

1. Introduction:

Insulin is the hormone that causes major pathogenic difficulties such as diabetes mellitus, which has become a global problem in both developed and developing countries.[1] Insulin deficiency or low levels cause glucose reuptake to be reduced in most body cells, and it is also responsible for signaling to other body systems.[2] Lifestyle changes, insulin resistance, generalised obesity, and other diabetes risk factors may be responsible for a variety of complications such as neuropathy and vasculopathy.[3] Subcutaneous insulin delivery has a variety of drawbacks, such as itching, allergic responses, and local pain, and to address these issues, insulin delivery channels have been expanded to include oral, transdermal, nasal, rectal, pulmonary, and implant delivery.[4,5]

Because insulin is a peptide hormone, it is destroyed by gastric acid when consumed orally. Insulin absorption through the skin is unreliable, and it cannot be used to simulate physiological insulin secretion. Furthermore, intradermal, intramuscular, and intravenous therapy are not appropriate for daily self-administration. Because of the convenience of self-injection, the subcutaneous route of administration is extensively used for insulin delivery. It has drawbacks such as injection site discomfort, lipodystrophy, and patient noncompliance, among others.[6] The goal of the latest insulin administration technologies is to give insulin with minimal invasiveness, accuracy, and precision while

reducing patient burden.

Diabetes is derived from the Greek term 'Siphon,' and in the early nineteenth century, it was thought that diabetes mellitus was caused by a malfunction of the digestive system linked to the pancreas, as well as controlled carbohydrate metabolism, according to the hypothesis.[7,8] Children with diabetes had a short life expectancy, and the prognosis for adult-onset diabetes was terrible, but the above diet allowed them to live for several years. 10 Insulin was first made using Islet cell extracts, which failed due to purity issues, but it was later proven to be a successful discovery, and Banting was awarded the Nobel Prize in Physiology or Medicine in 1923. [9]

Insulin is a protein made up of three chains of amino acids: A Chain (21 amino acid residues), B Chain (30 amino acid residues), and C Chain (which joins A and B). Insulin is released once Pro-insulin is broken down. Insulin monomers have a proclivity for forming dimers and hexamers.[10,11] Insulin is produced in the -cell of the pancreas as a pre-curser known as Pre-pro-insulin, and the genes responsible for this are located on chromosome 11-which is adjacent to the factor IGF2. 14 Micro-vesicles transport pro-insulin with a C chain into the Golgi apparatus, where it is released by pro-hormone convertase 2 and 3 and carboxy peptidase; the conversion of pro-insulin to insulin continues in developing granules. [11]

Insulin glulisine, the most recent rapid-acting insulin analogue, was introduced in 2004, with asparagine replaced by lysine at position 3 and lysine replaced by glutamic acid at position 29. Its activity was discovered to be identical to that of insulin lispro. [12, 13] Insulin glargine was found to be the first long-acting man-made version of human insulin analogue. Chain-A is elongated by the addition of two arginine residues at the carboxy terminus, and chain-B is elongated by the addition of two arginine residues at the carboxy terminus. It works by replacing the insulin produced regularly in the body, assisting in the movement of sugar from the blood into other tissues, and preventing the liver from creating excessive amounts of sugar. [14, 15]

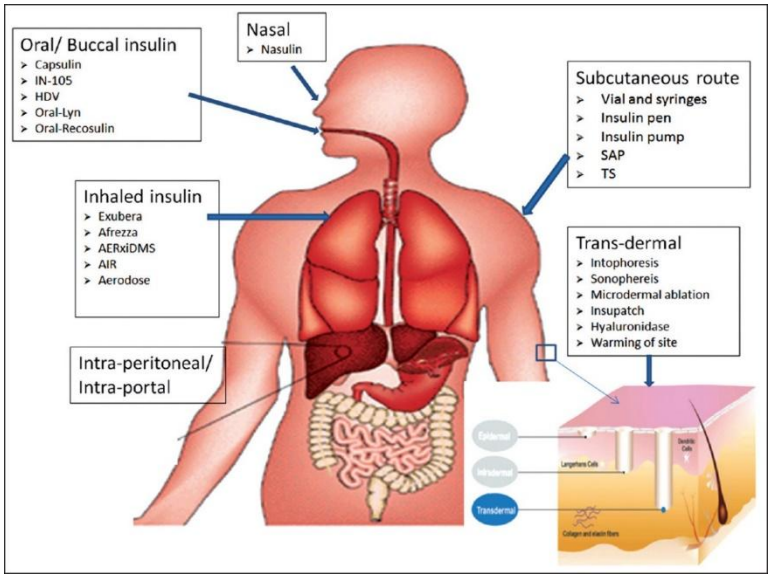
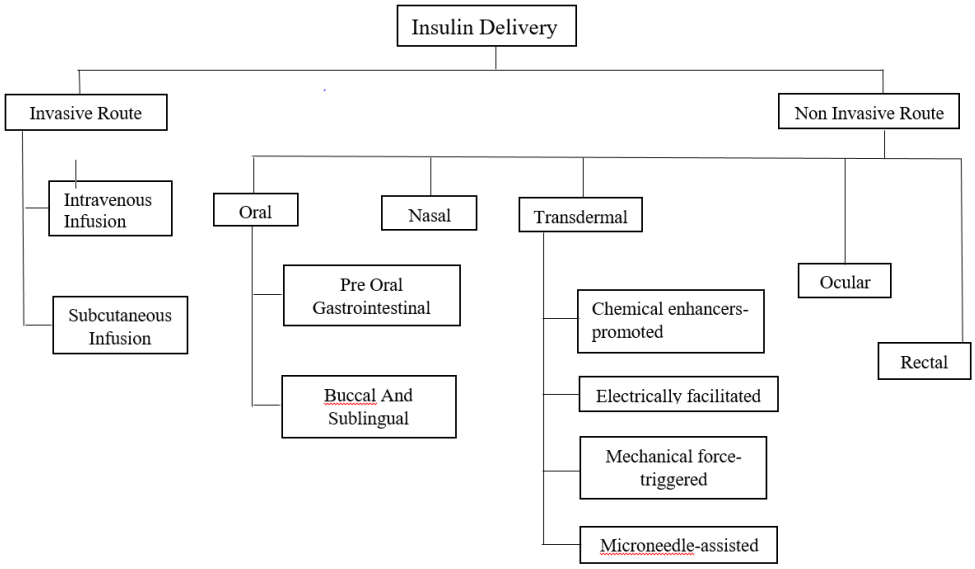


Fig.1: Novel Routes of Insulin Administration

Insulin and its analogues are utilised for a variety of purposes, including blood glucose control, wound healing, common parenteral feeding, anti-aging, cell culture and organ preservation, and the avoidance of septic shock. **[16, 17]**

2. Novel Routes of Insulin Delivery:



2.1. Invasive Route:

2.1.1 Intravenous Infusion:[149]

Intravenous (IV) insulin therapy involves injecting insulin straight into a patient's bloodstream. It could be used by healthcare experts to treat persons with high blood sugar levels. IV insulin therapy is a fast and reliable approach to inject insulin into the bloodstream. IV insulin therapy is a good treatment for hyperglycemic crises because of its fast-acting nature.

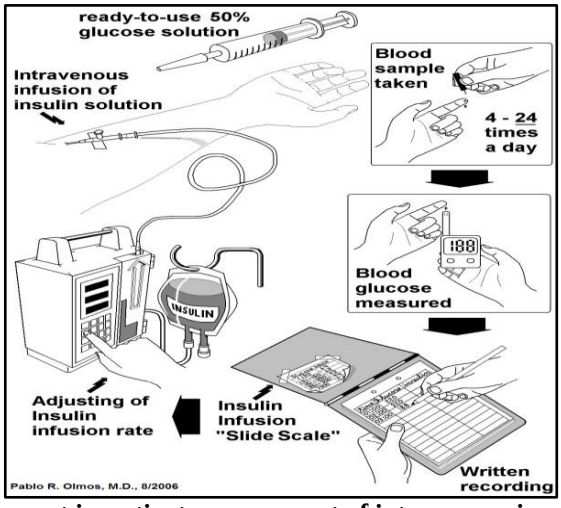


Fig.2:Current in-patient management of intravenous insulin infusion

IV insulin therapy entails putting a thin tube into the arm, which doctors refer to as a catheter. The catheter will be attached to a vein via a needle inserted by the doctor. A bag containing insulin and other liquids, such as saline, is connected to the catheter. The length of time a person needs IV insulin is determined by their blood sugar levels. Trusted Source says that IV insulin therapy can last anywhere from 3 to 12 hours. Throughout this time, healthcare personnel will check the person's blood sugar levels to ensure that they do not go too low.

2.1.2 Subcutaneous Infusion:

Insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII), is currently in its fifth decade of usage and is gaining popularity. More recently, continuous glucose monitoring (CGM) devices have been integrated onto the pump screen, and the first FDA-approved insulin pump that responds to sensor data to adjust basal rates, suspend on low or impending low, and give automatic correction bolus doses when glucose is approaching pre-determined targets has been developed. Glucose management is being revolutionised by automated insulin delivery systems. [144,145] According to current data, about 1 million persons with diabetes use insulin pump therapy around the world. [146]

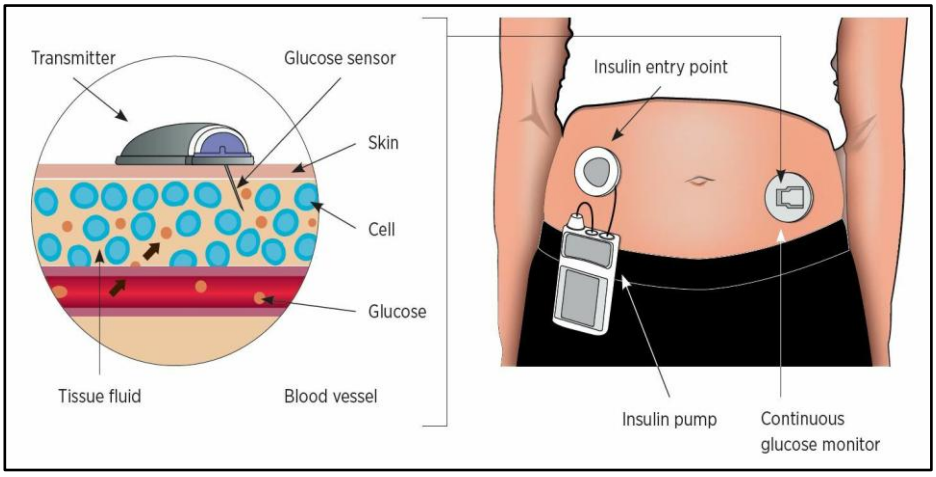


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Fig.3: Subcutaneous Infusion (Infusion Pump)

❖ **Infusion Set Selection:**

Infusion sets and set insertion devices, such insulin pumps, are more suited to specific individuals. Many pumps offer a number of infusion set options, while others employ proprietary sets that can only be used with the manufacturer's pump. To select the proper type of infusion set, a preliminary assessment of body composition and lifestyle is required. [147]Teflon cannula vs. metal needle, tubing and cannula or needle length, disconnect and insertion mechanisms, angle of insertion, adhesion, and aesthetics are all factors to consider when choosing an infusion set. [148] a "default" infusion set will be delivered if an infusion set is not specified when the insulin pump is ordered. The use of an infusion set that isn't well matched can cause dissatisfaction and lead to the abandonment of insulin pump therapy.

2.2 Non Invasive Route:

2.2.1 Oral Insulin Delivery:

Oral insulin delivery via the gastrointestinal tract (GIT) has the highest patient compliance and avoids the discomfort and drawbacks of insulin delivery via the subcutaneous route. Furthermore, the oral method of insulin delivery is simple to use, removes the pain associated with injections, reduces the risk of infection, enhances absorption, and closely resembles the natural route of insulin secretion. [18] Oral insulin, like endogenously generated insulin, is transported directly into the liver via portal circulation. [19]

Fig.4: Insulin Tablet

2.2.1.1 Challenges in oral insulin delivery via GIT & possible approaches to solve them

Most oral protein-based medicines, such as insulin, have a bioavailability of less than 1% at the moment. As a result, the primary goal of protein-based medicine oral delivery is to increase bioavailability to 30–50% [20]. There are various obstacles to overcome when it comes to enhancing insulin bioavailability. The following is a list of patents that describe methods for overcoming problems in insulin delivery by mouth.

a. Enzymatic & pH degradation of insulin in the GIT:

Insulin is rapidly degraded in the stomach and gastrointestinal tract (GIT) due to enzymatic activity and severe pH conditions. Insulin is degraded in the GIT by pepsin and pancreatic proteolytic enzymes such trypsin and -chymotrypsin. [21] Insulin is degraded in the stomach by acid, luminal degradation in the intestine by luminal degradation, and intracellular breakdown by intracellular degradation.

❖ **Protection from pH denaturation & enzymatic degradation in the GIT.**[22]

Universidade of Coimbra employs calcium carbonate as an immobilising agent and gelled submicron insulin particles immobilised within a sodium alginate matrix. They are covered with two layers, each of which is capable of increasing insulin absorption across intestinal mucosal tissues while also blocking digestion by gastric enzymes.

Hydrogels are cross-linked networks of hydrophilic polymers that can swell in response to changes in pH. These polymers have lower swell ability indices in the stomach's lower pH, but higher

swell ability indices in the intestine's higher pH. These polymers' pH-dependent swelling ability makes them ideal insulin carriers in the GIT.

Liposomes are vesicles composed of one or more lipid bilayers sandwiched between water compartments. To protect medications from enzyme attack in the GIT, these vesicles encapsulate both hydrophobic and hydrophilic pharmaceuticals. Because liposomes are often unstable, they must be lyophilized before being stored for long periods of time. Insulin can be prepared in the form of liposomes to shield it from enzymatic damage inside the GIT. SDG, Inc. (an Ohio Corporation) presents a technique for making orally accessible insulin formulations from variously sized liposome constructions, such as liposome fragments, lipid particles containing insulin, gelatin, and biotin targeting agents.

b. Poor transport of insulin across the epithelial cell membrane:

Oral medicines are absorbed in the GIT in one of two ways: transcellular or paracellular. [23] The permeability of a drug molecule's passage via a tight junction from apical to basolateral compartments in the paracellular route is determined by its permeability through the tight junction. Insulin has a low lipophilicity of about 0.0215 for octanol–water partition coefficient. Furthermore, because insulin's isoelectric point is around 5, it is negatively charged at the neutral pH of the small intestine. As a result, getting through the cell membrane is difficult. Because there is little indication of active insulin transport over the intestinal mucosa [24], the aqueous paracellular pathway is the predominant route for insulin transport across the epithelium. [25]

The use of permeation enhancers can boost insulin absorption through the GIT. Permeation enhancers boost oral drug absorption in the GIT by disrupting the cell membrane or modulating tight junctions with tight junction agonists. [26] Surfactants, bile salts, fatty acids, and biomolecules like chitosan are commonly employed in oral medication formulations as penetration enhancers. [27] Permeation enhancers help paracellular drug uptake by opening up the tight connections of the cell membrane.

c. Receptor-mediated degradation:

The creation of insulin receptor complexes activates glucose absorption by cells. The insulin receptor is a transmembrane protein that belongs to the tyrosine kinase receptor family [28]. Insulin binding to the insulin receptor initiates glucose uptake in healthy people, but its malfunction leads to diabetes and cancer. [30, 29] The insulin receptor complex is taken within the cells through endocytosis

and destroyed by insulin-degrading enzymes after insulin has completed its activity. Insulin's bioefficacy and bioavailability can be improved by reducing receptor-mediated degradation.

The insulin–betaine combination is used by Bio Ethic to reduce receptor-mediated degradation. Betaines are positively charged N-trimethylated amino acids. Because the negatively charged insulin forms a covalent connection with the positively charged betaine, the receptor binding capacity is reduced and receptor-mediated degradation is reduced.

d. Dosage-form stability:[31]

Microemulsion and Nano emulsion preconcentrates are self-microemulsifying drug delivery systems (SMEDDs) and self-nanoemulsifying drug delivery systems (SNEDDs). Isotropic mixes including a surfactant, a solubilizing agent, oil, and excipients are known as SMEDD or SNEDD formulations. When SMEDDs or SNEDDs come into contact with water, they generate microemulsions or nanoemulsions (with or without agitation). SMEDD and SNEDD formulations are thermodynamically stable and improve oral medication bioavailability and solubility. Despite the fact that SMEDDs and SNEDDs are known to boost the bioavailability of hydrophobic medicines, insulin (a hydrophilic peptide) is difficult to prepare due to its low solubility.

SMEDD or SNEDD formulations are used by Novo Nordisk for oral insulin administration. Insulin, a semipolarprotic organic solvent (e.g., glycerol or propylene glycol), and two nonionic surfactants with a hydrophilic–lipophilic balance of greater than 10, such as C8 fatty acids (caprylates), C10 fatty acids (caprates), or C12 fatty acids (laurates). To maximise drug loading capacity and bioavailability, the hydrophilic–lipophilic balance of the two nonionic surfactants was kept above 10.

2.2.2. Inhaled Insulin Delivery:

Insulin was originally delivered to the lungs as an alternative to subcutaneous injection. Insulin administration by aerosol has long been known to lower blood glucose levels. [32] Early research found that giving bovine or porcine insulin through nebulizer caused immediate hypoglycemia in diabetic and non-diabetic subjects. [33,34]

The pulmonary route has several advantages, including a large and well-perfused absorptive surface, the absence of particular peptidases that break down Insulin in the gastrointestinal (GI) tract, and the capacity to skip "first pass metabolism." [35] However, the actual mechanism of insulin absorption across the pulmonary epithelium is unknown, but transcytotic and paracellular pathways are thought to be involved.[32]

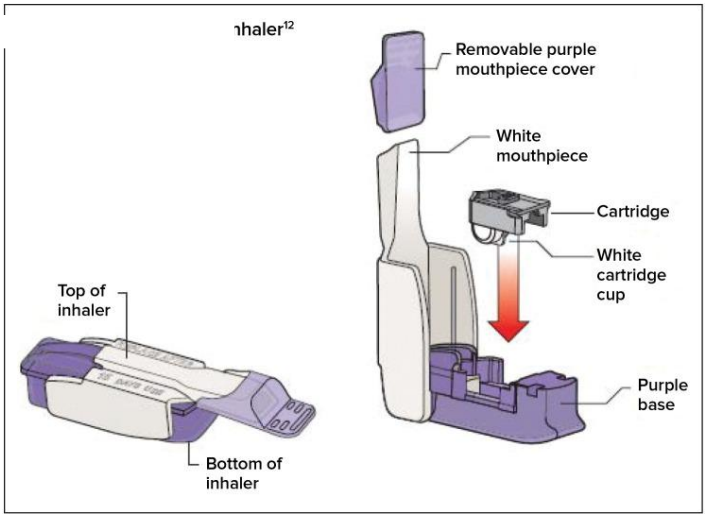

Fig.5:Afrezza Insulin Inhaler

Exubera, the first inhalation product, was approved by the US Food and Drug Administration in 2006. Exubera was a dry power formulation that came in 1 mg and 3 mg doses and was administered by an Inhance inhaler. Exubera was discovered to exhibit pharmacokinetic and pharmacodynamic qualities (PK/PD) similar to insulin, with a faster onset of action (10-15 min). [37]Exubera was reported to dramatically lower postprandial blood glucose and A1c in patients with uncontrolled T1DM and T2DM in clinical trials. [38]Exubera, on the other hand, was not recommended for smokers because it raised the risk of hypoglycemia due to greater absorption than nonsmokers. [39]Patients were also obliged to have pulmonary function tests before starting medication, after 6 months, and once a year after that. [39] Despite the noninvasive method, this medication did not do well commercially, presumably because to greater costs, a large delivery device, worries about diminishing pulmonary function, and a lack of desire by patients and clinicians. Pfizer removed this medicine from the market in 2007.

Newer inhalational devices being studied in clinical trials include the AERx insulin Diabetes Management System, Aerodose, ProMaxx (protein matrix microsphere), and advance inhalational research. [40]Sanofi has launched Afrezza in the United States for the management of diabetes in patients with T1DM. Although the pulmonary route of insulin delivery is noninvasive, it is constrained by technological challenges with inhaler devices, greater costs, and long-term safety, particularly with regard to pulmonary function.

2.2.3. Transdermal Insulin Delivery:

In comparison to painful hypodermic injections, a transdermal delivery technique that delivers insulin over the epidermal barrier is a minimally intrusive and appealing method for insulin delivery.

[42, 41] It also provides a number of advantages over other methods of administration, including as oral, pulmonary, and nasal. Insulin given via a transdermal method, for example, is able to prevent chemical and enzymatic breakdown in the gastrointestinal tract. [43] This method can also produce a sustained release, allowing therapeutic concentrations to be maintained for longer periods of time. [44] Finally, the ease with which this administration is carried out may boost patient adherence, resulting in better glycemic control. [44]

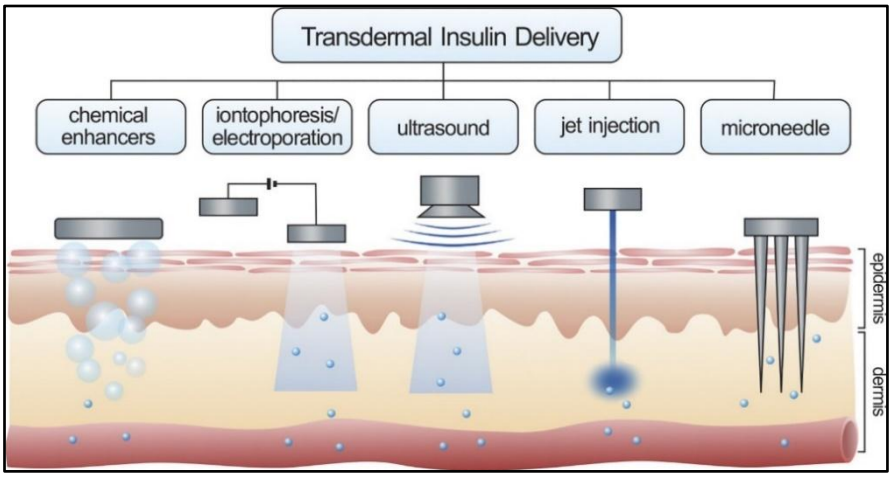

Fig.6: Different Routes of Transdermal Insulin Delivery

However, due to the intact skin's intrinsic, protective qualities, efficient insulin delivery via the skin remains a challenge. Low-molecular-weight therapeutics (less than 500 Da) can easily enter the skin, whereas the passive transport of higher-molecular-weight protein medicines, such as insulin, is severely limited. [45] Various techniques to physically or chemically boost the transport efficiency of the insulin molecule across the skin have been studied to overcome skin barriers in transdermal insulin delivery. Chemical enhancer-assisted, electrically facilitated, mechanical force-triggered, and microneedle (MN)-assisted techniques are all discussed in this study. The difficulties that may arise in the development of prospective clinical applications are also explored.

2.2.3.1. Chemical enhancers-promoted transdermal delivery:

Chemical penetration enhancers that can breach the skin barrier and offer an additional driving force for delivering medicines have been extensively studied in order to improve skin permeability. [46, 47] Traditional chemical compounds, as well as membrane-permeable peptides and vehicles, are all efficient chemical enhancers. Chemical enhancers can be inserted into the stratum corneum's highly organised lipid bilayer to disorganize molecular packing or remove lipids to cause nanometer-sized lipid-packing defects, resulting in increased insulin transport efficiency. [48, 49]

Previously, the Gasem group looked into the permeability enhancement capabilities of 43 distinct chemical enhancers utilised in insulin administration. [50] The authors also highlighted possible criteria for further enhancer screening. Iodine, according to Sintov et al., increased insulin delivery through the skin by inactivating endogenous sulfhydryls such glutathione and gamma-glutamylcysteine, minimising the formation of disulfide bonds and preserving the potency of insulin during its flux from the skin into the circulation. [51]The ability of trypsin to react with the stratum corneum was also investigated for improved transdermal insulin delivery. It was discovered that trypsin changed the protein structure of the stratum corneum from alpha to beta and reduced skin electrical resistance, resulting in a 5.2-fold increase in insulin absorption (insulin at pH 3). [52]

Chemical enhancers have also been investigated using nano/micro vesicles such as liposomes and nano/microemulsions. They can promote skin permeability as well as act as carriers for medication solubilization and delivery through the skin. [53, 54] Various nanocarriers, such as lipid-based vesicles, CaCO3 nanoparticles, and Nano emulsions, have been shown to encapsulate and transdermally transfer insulin into the dermis. [55, 56] For example, King et al. discovered that lipid-based biphasic vesicles can improve insulin administration through skin penetration. [57]These researchers created a transdermal patch with insulin-encapsulated biphasic vesicles and applied it to the abdominal skin of diabetic mice for 48 hours. The animals responded to the patch loading 50 mg vesicle entrapped insulin for over 51 hours, with a 43 percent reduction in blood glucose. In a diabetic rat model, further investigation of the topical administration of biphasic vesicles revealed that the lymphatic route was predominantly responsible for insulin transport and absorption. [58]

To supply the drug concentration-gradient driving force, chemical penetration enhancers can disturb the skin structure to boost permeability and improve drug solubility. Despite this, several chemical enhancers have limited insulin transdermal delivery efficiency. How to keep the most potent chemical enhancers from diffusing out of the stratum corneum and causing discomfort in deeper tissue should be explored further.

2.2.3.2. Electrically facilitated transdermal delivery:

Electrical tools that aid insulin transport through the skin have gotten a lot of study in addition to chemical penetration enhancers.[59,60] These electrical instruments, unlike pharmacological penetration enhancers, improve insulin delivery efficiency through the skin by supplying additional driving force via electrical interactions or generating temporary disruption of the stratum corneum by a high-voltage electrical pulse.

a. Iontophoresis:

In the early twentieth century, iontophoresis became popular as a transdermal augmentation technique. The delivery of big and/or charged molecules is accomplished using a modest electric current. [61, 62] This method uses a pair of electrodes put on the skin to create an electrical potential between the skin's surface and the capillaries beneath it (Fig. 3). The positive electrode drives positively charged therapeutic molecules toward the capillaries from the skin surface, while negatively charged molecules travel through the skin to the negative electrode. Electromigration and electroosmosis have been recognised as two of the most important driving mechanisms affecting the transport of medication ions over the skin into systemic circulation.[63]The amount of charge carried is determined by the intensity of the electric field and the length of treatment. Nonetheless, because the skin is negatively charged in the physiological state, it is permselective to cations when exposed to an electric current. [64] The negative charge of human insulin (5800 Da) at physiological conditions makes transdermal delivery of insulin to therapeutic levels difficult. The most effective condition for regular insulin iontophoresis, according to Siddiqui et al., was to adjust the aqueous solution of concentrated insulin (500 IU/ml) to a pH of 3.7. [65]Pillaiet al. also discovered that anodal iontophoresis of insulin at pH 3.6 improved insulin stability and permeability. Using charged liposomes as carriers during iontophoresis, Kajimoto et al. aimed to improve insulin transfer efficiency. [66] The transdermal iontophoresis (0.45 mA/cm2 for 1 h) of cationic liposome-encapsulated insulin through the transfollicular pathway resulted in a steady drop of 20% in BGLs at 18 hours after delivery, which was maintained for up to 24 hours in a diabetic rat model. A matching increase in plasma insulin levels (1.4 ng/mL 18 hours after treatment) was also seen, which was higher than that seen in rats treated with intraperitoneally injected insulin.

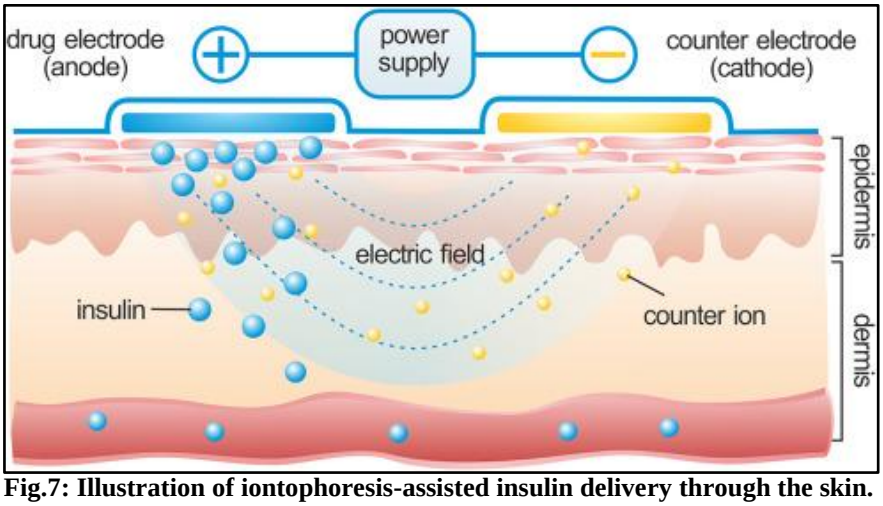

Fig.7: Illustration of iontophoresis-assisted insulin delivery through the skin.

To reduce the risk of electrochemical damage, such as burns and skin irritation, during iontophoresis. [67] Alternating current iontophoresis was compared to direct current iontophoresis, and it was shown to have less negative effects. [68] According to feasibility experiments, alternating current iontophoresis-activated transdermal insulin administration systems delivered 57 percent of the initial insulin dose (2.85 mg in a 500 mL sample). [69]

Iontophoresis, unlike chemical penetration enhancers, does not damage the skin's structure, which could compromise its barrier function. Despite this, the low-level current used in such a procedure reduces the efficacy of insulin transport via the stratum corneum. Although a higher delivery rate can be achieved by increasing current intensity, the risk of skin irritation and pain restricts the maximum current intensity.

b. Electroporation:

Another appealing option for electrically assisted transdermal medication delivery is electroporation. Electroporation is a process that uses short, high-voltage pulses to create transitory disturbance in the stratum corneum by establishing micro-pathways across its lipid bilayers, as opposed to the continuous application of low-level current (hours) in iontophoresis. [70] The stratum corneum is the primary barrier and accounts for the majority of the skin's electric resistance (5-25 k/cm2). [70] Electroporation is the application of high voltage pulses that are higher than the stratum corneum's breakdown potential (75-100 V), resulting in the development of temporary pores in the stratum corneum's lipid bilayers, which enable drug transport over the skin. [71, 72]

Several investigations have been conducted to confirm that electroporation improves insulin transdermal delivery. In rabbits, Mohammad and colleagues looked into the effects of different electroporation parameters (number of pulses, insulin concentrations, and field strengths) as well as chemical enhancers (castor oil, iodine, and oleic acid). [73]Rastogi et al. investigated electroporation of polymeric nanoparticles encapsulating insulin, demonstrating a 4-fold increase in insulin deposition in rat skin compared to free insulin electroporation, as well as a therapeutic effect that lasted from 24 to 36 hours. [74]Sen et al. described a new transdermal enhancement strategy that involved combining anionic lipids with target molecules and was found to improve the electroporative transport of negatively charged permeants up to 10 kDa in size. [75] The increased quantity and size of the electropores generated during electroporation in the presence of the lipid dispersion, as well as their longer lifetime, were attributable to the enhancing effect. Anionic lipids, in particular, were found to

have a positive effect in lowering skin resistance and delaying skin resistance recovery following pulse application, extending the potential of lipid-enhanced electroporation for delivering big biomolecules.

More recently, these researchers investigated the effect of another anionic lipid, 1,2-dimyristoyl-3-phosphatidylserine (DMPS), on the transdermal transport of insulin using a porcine epidermis model and found a 20-fold increase in insulin with dispersion in DMPS electroporation for 10 minutes (100-105 V, 1 ms pulse width at 1 Hz) compared to that without DMPS. [76]

Sen and colleagues also demonstrated a synergistic effect of combining DMPS and anodal iontophoresis (electroosmosis) with electroporation on insulin transport both ex vivo and in vivo, with the combination treatment of DMPS (in 0.2 percent sodium dodecyl sulphate) and electroosmosis resulting in a ten-fold increase in plasma insulin level in a Sprague-Da [77, 78]Sugibayashi and coworkers used human insulin to validate this in vivo synergistic treatment of electroporation and iontophoresis. [79] In their work, this group found that insulin had varied aggregation properties at different pH levels: insulin at pH 10 had a larger ratio of nonassociation formulation, whereas insulin at pH 7 had a higher ratio of hexamers. As a result, with pH at 10, a considerably higher plasma level of insulin was discovered compared with pH at 7.

2.2.3.3 Mechanical force-triggered insulin delivery:

Mechanical force, in addition to electrical fields, can be used to create temporary channels on the skin's surface for transdermal medication delivery. [80] Ultrasound and jet injection are two examples of mechanical force-triggered insulin delivery systems. By causing heat or cavitation, ultrasound can improve medication permeability across the skin. The high-speed liquid is used to disrupt the skin's surface, allowing the insulin solution to be dispensed into the skin tissue.

a. Ultrasound:

Ultrasound, which is a longitudinal sound wave with a frequency greater than 20 kHz, has been employed in biomedicine since the turn of the century for imaging, ablation, shattering kidney stones, and facilitating transdermal medication distribution. [81,82] Ultrasound-induced hyperthermia or cavitation has been found to increase skin permeability to medicinal substances by increasing mechanical force. [83,84] The use of ultrasound for drug delivery through the skin is known as sonophoresis, and the frequency range used varies between 20 kHz and 16 MHz. When compared to passive diffusion, high frequency sonophoresis (HFS) (700 kHz) was initially researched primarily for transdermal drug administration, with typical skin penetration enhancements between 1 and 10 folds. [85, 86]

Scientists improved their understanding of the cavitational consequences of sonophoresis in the early to mid-1990s. Low-frequency sonophoresis (LFS) (20-100 kHz) was shown to be more effective than high-frequency sonophoresis (HFS) in increasing skin permeability. In mice and rabbits, Tachibana and colleagues used ultrasonic with a frequency of 48 kHz or 105 kHz to achieve higher insulin transport through the skin than passive diffusion, resulting in a considerable reduction in BGLs. [88,89]Mitragotri et al. also shown that LFS-mediated transdermal transport of proteins such as insulin, interferon, and erythropoietin was successful. [90] Their tests in a diabetic rat model demonstrated that LFS provided sufficient insulin delivery, with BGLs dropping from 400 to 200 mg/dL in 30 minutes.A further study found that LFS at 20 kHz was up to three orders of magnitude more effective at increasing skin permeability than HFS at 1 MHz. [91] LFS-mediated transdermal insulin delivery has been intensively studied since then. Boucaud et al. shown that using LFS (20Hz) could provide quick, repeatable, and reversible insulin transdermal delivery in rats and neonatal pigs. [92,93] They also found that the amount of insulin carried through the skin of rats was proportional to the energy dose and duration of an ultrasonic pulse, indicating that the cavitation-related mechanism was at work. [94]

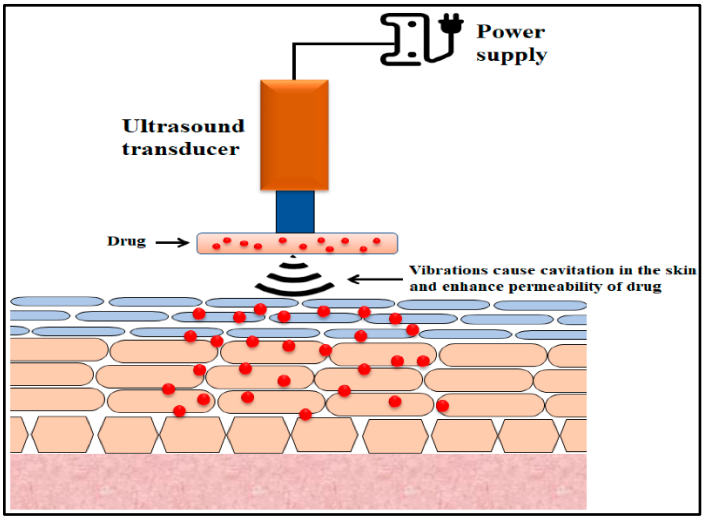

Fig.8: Insulin Delivery through Ultrasound

In vivo animal investigations have shown that ultrasound-mediated transdermal medication delivery has clinical potential in the delivery of tiny macromolecules such as insulin. HFS, on the other hand, may cause harm to deep skin tissue, and LFS frequently necessitates the use of a matching medium or scaffold, such as hydrogel, Nano-network, and cells, that is injected invasively into skin tissue. Furthermore, the use of advanced equipment is restricted for patients with diabetes.

b. Jet injection:

Another needle-free method for transdermal insulin delivery is jet injection. Instead of using solid syringes, the jet injector uses a high-speed narrow spray of insulin to create a tiny hole in the skin that allows the insulin to pass through. [95,96] Similar to hypodermic injection, jet injection has been linked to a high delivery efficiency of over 90%. Furthermore, using jet injectors to administer insulin results in a faster on-set of plasma insulin. [97,98] Wit et al. showed that jet injection can quickly treat severe hyperglycemia in diabetic patients who are overweight or obese. [99]Furthermore, because jet injection delivers insulin across a greater region of skin tissue than conventional injection, the pharmacokinetics of this method of insulin administration are more similar to pancreatic endogenous insulin production. [100]Guo et al. evaluated postprandial glucose control achieved with a jet injector to an insulin pen and discovered that the jet injector's increased insulin absorption is advantageous for postprandial blood glucose regulation. [101]

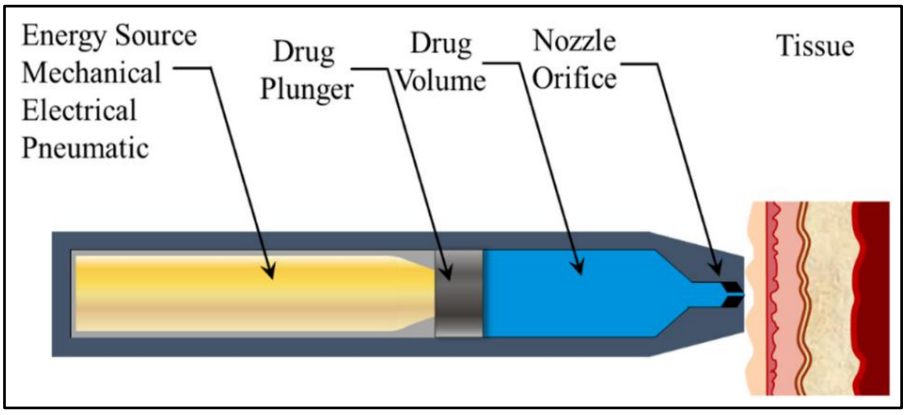

Fig.9:Jet Injection

Despite the benefits indicated above, the current application of jet injection technology is hampered by a number of problems. Although liquid jet injection technology eliminates the need for needles, the massive volume of high-pressure spray can cause bruising, bleeding, and pain. [102,103,104] According to studies, jet injectors are no less painful than hypodermic needles. Mitragotri and colleagues devised a microjet injection device that only injects solution volumes in the nanoliter range to reduce the risk of adverse responses. [105]They claimed that insulin was delivered into the skin without deep penetration in a rat model using pulsed microjets, which could potentially reduce pain and bleeding. Furthermore, the combination of biodegradable particles with insulin to achieve a continuous and regulated release of insulin may improve the application of jet injection. When Mitragotri and colleagues tested the ability of jet injectors to deliver polymeric nanoparticles through the skin, they discovered that the nanoparticles did not penetrate the skin as deeply as previously

thought, but that they could release cargoes for longer periods of time.[106] Several jet injectors are commercially available, but they have not been widely adopted. Jet injectors' cost, size, and performance may be modified in the future to make routine use easier.

2.2.3.4 Microneedle-assisted transdermal delivery:

Microneedle (MN) approaches have recently emerged as an alternate method for transdermal protein delivery. The micro-scaled needles can penetrate the stratum corneum and reach the epidermal and dermal layers without causing pain. [107,108] MN creates temporary micro-channels for drug transport, but they immediately heal after MN is removed, preventing long-term skin tissue injury. [109,110]

Based on the material of the MN and the mechanism of drug delivery, the MN device is classified into different types (Fig.).

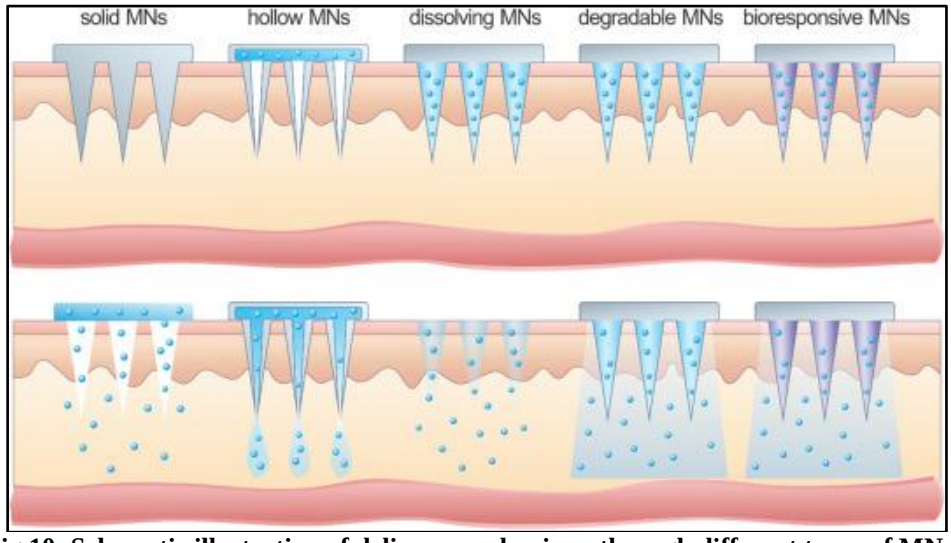

Fig.10: Schematic illustration of delivery mechanisms through different types of MNs.

Solid MNs are made of polymers with encapsulated drugs and are designed to pierce the skin to improve drug transport; hollow MNs are made of polymers with encapsulated drugs and are used to inject a fluid drug formulation through the opening on the skin caused by needles; and dissolving or degradable MNs are made of polymers with encapsulated drugs. We also go over some newly created bioresponsive MNs that can adapt to physiological glucose levels and release insulin on-demand.

a. Solid Microneedles:

Skin perforations from solid MNs were frequently used in the early generation of MN-aided insulin delivery, sometimes known as "poke with patch." [111]In this method, MNs penetrate the skin to produce microchannels via which insulin can be delivered once a patch or topical solution is applied. During the last few decades, a slew of research have been published that show efficient insulin administration through the skin.

MNs, for example, were used by Prausnitz and colleagues to establish the hypoglycemic impact of insulin in diabetic rats. [112] A laser-cut array of 105 microneedles was placed into the skin of diabetic rats, following which insulin solution was delivered in contact with the skin for 4 hours. In vivo, these solid metal MNs showed up to an 80% decrease in BGLs and improved transdermal insulin delivery.

Solid MNs were recently improved by coating payloads directly onto the surface of MNs to control and maximise the delivered insulin dose. In theoretical models, Al-Qallaf et al. investigated insulin concentration patterns in blood using drug-coated microneedles of various shapes and dimensions. **[113]**The results of the simulations showed that rocket-shaped MNs were able to achieve the highest insulin concentration.

b. Hollow Microneedles:

Hollow MNs are designed to allow medications to be delivered into the skin through the needle's inside. Prausnitz and colleagues used microinfusion to inject insulin into diabetic rat skin through hollow glass MNs, leading in a consistent drop of up to 70% of preinfusion BGLs during a 5-hour period. **[114]**They also created hollow metal MN arrays for transdermal insulin delivery, which they designed and built. The mechanical test revealed that these MNs were capable of piercing the entire skin surface without breaking. Furthermore, silicon hollow MNs have been investigated for insulin administration. **[115,116]**

Human investigations have also looked into the delivery efficacy of hollow MNs. Gupta et al. originally looked at how hollow metal MNs delivered insulin transdermally to two type 1 diabetic adults. **[117]**To manage the insulin infusion rate, an insulin pump was attached to the MNs and subsequently applied to the belly skin. With the insertion of MN in a depth of 1 mm within the skin, the results showed quick insulin absorption and a decrease in BGLs. Human clinical trials have also been conducted to assess the safety and efficacy of hollow MNs for insulin administration. **[118]**

c.Dissolving Microneedles:

Aside from insoluble metal and silicon MNs, current research on biocompatible polymeric MNs, such as dissolving MNs, has gotten a lot of interest. **[119]**The soluble polymers prepare dissolving MNs, which encapsulate the medication in the matrix and can totally dissolve once introduced into the skin to release the medicine. The therapeutic period is determined by the polymer material's dissolving rate, which can be modified from minutes to hours to satisfy treatment objectives. **[120]** Furthermore, using biocompatible polymers could eliminate the creation of sharp biohazardous debris. **[121,122]**

Various dissolving MNs composed of sugar glass polymers, such as maltose, trehalose, and have been described to date. After insertion, sugar glass MNs usually disintegrate fast in human skin. [123,124] The manufacturing of these MNs, however, necessitates a high temperature of above 100 °C to induce rubber to glass transitions of sugar glasses, which may harm the bioactivity of biomolecules such as insulin. [125]To solve the thermal problems of the melting fabrication process, new fabrication techniques have been devised. Martin et al., for example, created dissolving MNs using a low-temperature processing approach. [126]

c. BioresponsiveMicroneedles:

Efforts to achieve glucose-responsive smart insulin delivery have recently gotten a lot of attention. [127]Bioresponsive MNs have been highlighted as a viable technique for glucose-regulated insulin delivery since they can adapt to physiological inputs. [128,129] Glucose-responsive components are typically combined with a polymeric MN matrix in this platform.

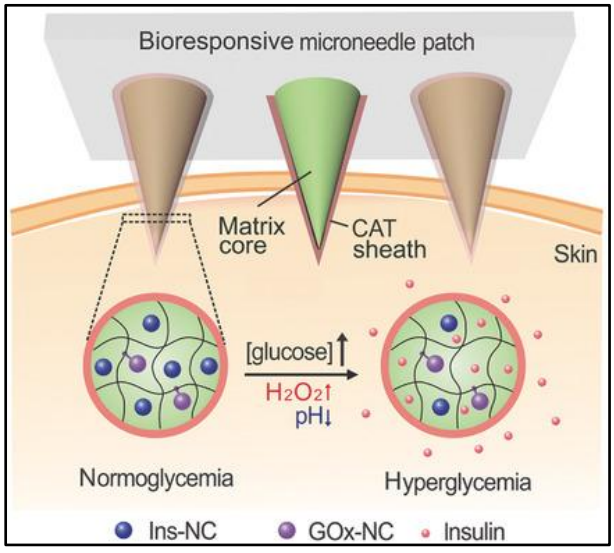

Fig.11:BioresponsiveMicroneedles

Yu et al. described a glucose-responsive MN patch made up of cross-linked HA matrix and hypoxia-responsive vesicles (GRVs) as a "smart insulin patch" in 2015, claiming that it was a painless and self-regulating modality. [130]The hypoxia-sensitive hyaluronic acid derivative (HS-HA), which contains a hypoxia-sensitive group, 2-nitroimidazole, self-assembled the GRVs (NI). The hydrophobic NI on HS-HA is reduced to hydrophilic 2-aminoimidazole under reductive circumstances, causing the nanovesicles to disassemble. The MNs were then implanted with GRVs encapsulating insulin and glucose oxidase (GOx) to detect high blood glucose levels in the dermis. The enzyme GOx, which converts glucose to gluconic acid, has been widely used as a glucose sensor. [131,132]

e. Degradable Microneedles:

The dissolution rate of polymers, which is usually fast, is directly related to the release dynamics of payloads from dissolving MNs. MNs with a longer degradation period are favoured as delivery devices for protein medicines that require continuous delivery to maintain a consistent therapeutic dosage. [133] Polymers with a higher molecular weight and crosslinking density have been found to produce longer insulin release as well as improved MN mechanical characteristics. [134,135]During the degradation process, medication is slowly released from biodegradable MNs by passive diffusion, with swelling of MNs potentially speeding up drug diffusion.

For example, calcium ion cross-linked alginate/maltose composite MNs for insulin delivery were investigated, with maltose added to increase the MN's mechanical strength. [136] The biodegradable MNs that resulted had a mechanical strength of 0.41 N/needle and inflated significantly in 5 minutes before dissolving in 40 minutes. When compared to a group of diabetic rats who were subcutaneously injected the same amount of insulin, the insulin-loaded MNs showed a sustained decrease in BGLs and maintained the pharmacological activity of insulin for a longer period.

2.2.4. Ocular Route of Insulin Delivery:

The dynamics of the lachrimal system determine the possibility of systemic distribution of insulin or any other water-soluble medication via the ocular route. The lachrimal system is made up of four different structures: lachrimal glands, lachrimalcanaliculi, lachrimal sac, and nasolachrimal duct. [137]The dynamic lachrimal process is a highly efficient and quick approach to produce tears and drain them from the eyes. As a result of this process, the eye has a tendency to keep the residence volume (steady state volume) of tear in the conjunctival cul-de-sac at around 7 pL at all times. [138]The usual tear turnover rate is around 16 percent every minute. [139]

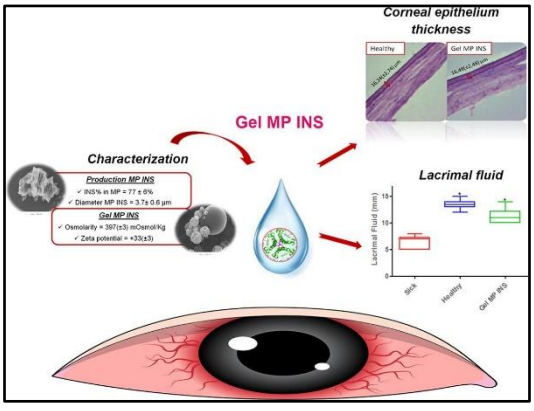

Fig.12: Ocular Route of Insulin Delivery

Although eye drops can deliver insulin to the eye, it is currently neither feasible nor regulated. The unpredictability of absorption is a key disadvantage of using insulin eye drops. Variances in application, fluid run-off out of the eye (spillage), fluid loss due to blinking, and differences in tear production rate are the main reasons of variation. This results in less than 5% bioavailability, with a lot of variance from patient to patient and day to day. Another disadvantage of eye drops is that they only work for a short period of time.

Tear fluid quickly washes eyedrops into the nasal meatus, resulting in fast absorption. Additional tears, on the other hand, quickly wash them away from the absorptive zone, and the unabsorbed insulin is swallowed and destroyed in the gastrointestinal tract. **[140]**

The use of an ocular device can solve difficulties including high variability, low bioavailability, short duration, and spillage in ophthalmic delivery. Insulin administration with an ocular device would be uniform because the device would only need to be implanted in the eye. Furthermore, an ocular device can be used to deliver a drug at a rate that ensures complete and long-term insulin absorption. **[140]**

The duration of insulin activity can be extended using a pharmacological carrier that operates as a controlled release method. This formulation can achieve therapeutic efficacy with a minimum dose of insulin while avoiding the systemic side effects of hypoglycemia by administering the medicine at an ideal rate. Furthermore, the frequency of dose for pharmaceuticals that require long-term administration, such as insulin, will be considerably reduced. In practise, the medicine is incorporated or encapsulated within a carrier, which is usually a polymeric material, to create the ocular device. **[140]**

2.2.4. Rectal Route of Insulin Delivery:

With a dose as low as 2 U/kg, **[141]**rectal injection of insulin via a suppository is successful in decreasing plasma glucose concentrations without impairments in rectal mucosae or other adverse responses. **[142]**We chose to deliver insulin by rectal suppository to normal and diabetic participants in view of the good findings observed in these experiments. The early investigations reported here were conducted to determine the efficacy of insulin suppositories in managing hyperglycemia in people with diabetes and to determine the feasibility of clinical application.

In normal and non-insulin-dependent nanobase diabetic patients, the efficiency of insulin administration through rectal suppository was investigated. When diabetic subjects were administered a 100-U insulin suppository (mean 1.8 U/kg), plasma glucose dropped four times as much as when

normal subjects were given the same dose (mean 1.6 U/kg). The insulin response after suppository injection had a strong positive connection with the plasma glucose level before administration (r = 0.83, P 0.01).Diabetic subjects who received a 100-U insulin suppository (mean 1.7 U/kg) 15 minutes after meals three times daily showed a significant (P 0.05) reduction in postprandial hyperglycemia, as well as a restoration of the normal circadian profile of plasma IRI and a decrease in urinary glucose from 26.59 to 2.01.0 g/day. There were no unfavourable reactions observed. Despite its limited bioavailability, these findings strongly suggest that the insulin suppository has a distinct feature. **[143]**

Porcine crystalline insulin (Nordisk Insulin Laboratorium Co., Ltd., Denmark) was combined with Witepsol H15 (Dynamit Nobel Co., Ltd., West Germany), a suppository base (polyoxyethylene-9 auryl ether, Nikko Chemicals Co., Ltd., Japan), and 0.02 M HC1 solution to make an insulin suspension. The insulin suspension was then cooled and hardened in a mould. With 3% (w/w) surfactant and 5% (w/w) HCl solution, the final concentration of insulin in a suppository was 50 U or 100 U/g. In the fasting state, the effect of rectal delivery of insulin suppository to normal and diabetic people. This study included six healthy volunteers aged 25 to 30 years old and five insulin-dependent diabetes individuals aged 44 to 60 years old.According to the findings of a 50-g OGTT, the diabetic participants were classed as non-insulin-dependent by the Japan Diabetic Society. Two diabetic patients were taking sulfonylurea at the start of the trial, but they quit 1 day before it began. There was no history of insulin injection in any of the participants. All of the participants were within 15% of their optimal body weight (Metropolitan Life Insurance Company Table, 1959). None of the patients reported symptoms of autonomic neuropathy. **[143]**

4. Conclusion:

There has been a long history of research aimed at finding a minimally or noninvasive insulin administration route that is effective, safe, convenient, and cost-efficient for patients. Each delivery method and route has its own set of benefits and drawbacks. Alternative routes of administration, if successful, could transform diabetes treatment and help patients enhance their quality of life.

To date, the numerous approaches that have been examined have incorporated strategies aimed at overcoming the intrinsic obstacles to protein uptake through the epidermis, gastrointestinal system, and nasal mucosa. Nonetheless, several of these approaches appear to have demonstrated their "proof of concept." However, pulmonary delivery appears to be the most therapeutically viable approach to date. Two of the pulmonary delivery devices are in phase III testing, and the findings so far show that they are equally effective as subcutaneous insulin.Before these devices may be used in the clinic, pulmonary safety and tolerability data must be established. Thus, two years after wishing for and

expecting "more physiological techniques for delivering insulin," procedures are in place to fulfil his wishes.

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149. Medically reviewed by Kelly Wood, MD — Written by Anna Smith "What to know about intravenous insulin therapy" on November 28, 2021