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AN UPDATE ON NEEDLE FREE INJECTION TECHNIQUE: A REVIEW

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ABSTRACT:

Needle-free injection technology (NFIT) is a large concept that includes a drug delivery system that delivers drugs through the skin using the principle of electrophoresis. The NFIT system was first introduced by Marshell Lockhart in 1936. The device is designed to avoid the problems associated with conventional needles by making them safe, less expensive, and more suitable. NFIT is easy to use, and there is no need for a skilled person. The key benefits include a very fast injection compared with conventional needles and no needle disposal issues. Many scientists are now working on technology that promises to deliver drugs more effectively and comfortably in order to have therapeutic benefits. The use of needle-free injection systems is an innovative technique to provide different medications to patients without puncturing their skin with a conventional needle. A brief description of the injection techniques, such as spring-loaded jet injectors, battery-powered jet injectors, and gas-powdered jet injectors, is also included in this article.

Key words: Needle free injection, Needle free technology, Needle free device, Safe, NFIT, Drug delivery.

I.INTRODUCTION:

Marshall Lockhart introduced the concept of needle-free systems in 1936. Then, Higson and other researchers in the early 1940s, created high pressure "guns" that pierced the skin with a thin liquid jet and deposited the medication in the underlying tissue.[1] NFIT (Needle free injection technology) is a needle-free drug delivery technique that works by impacting the skin with a high-speed stream of fluid to administer a drug while excluding vaccinations and systemically absorbed drugs like insulin [2]. The new technique for drug delivery is needle-free which is reusable and disposable device [3]. It includes the principle of electrophoresis for the delivery of medication through the skin. NFIT is easy to use and does not require any special expertise [4]. It is a unique way to administer medications to patients' systemic circulation. In general, needle-free injection delivers liquid media through a small hole at high pressure [5]. Disease is usually transmitted through injections when the needles are often reused or used in wrong way, so needle free injections are used. This is an alternative method of administering medicine to patients without puncturing their skin with traditional needles. [6] It is safe and less painful. The key benefits of a liquid jet injector over other delivery methods include its ease of use and the absence of the need for a needle. The advantages of this system are the elimination of broken needles, a more consistent delivery of medications and vaccines, and a reduction in the risk to worker safety. [7].

II.STRUCTURE OF SKIN:

For the right administration of medication through needle-free injection, the structure of the skin ought to be better-known.

The skin is one in all the body's major organs in terms of weight and expanse. The epidermis and dermis area unit the 2 layers that structure the skin. The hypodermis, usually referred to as body covering animal tissue, is found below the stratum.

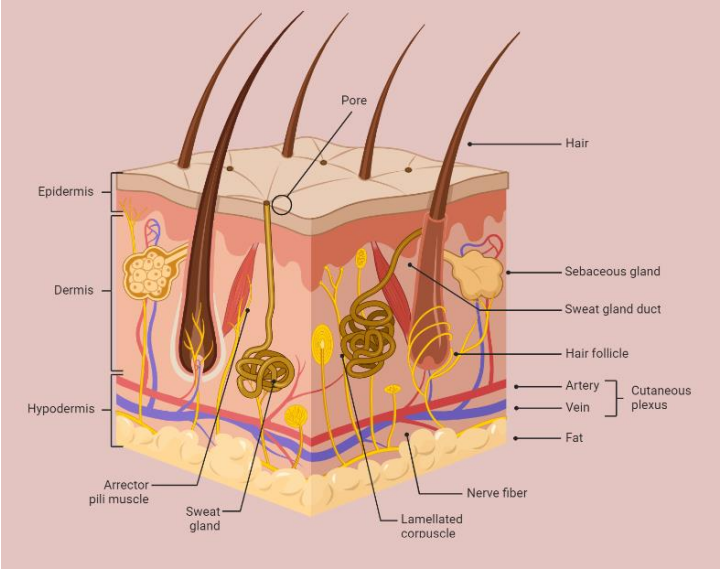

Fig.1 Structure of Skin

Epidermis:

The outer layer of skin is that the epidermis; it creates skin tone and may be a waterproof barrier. It's a basal plate beneath that's made from stratified squamous animal tissue. The epidermis lacks blood vessels, and blood capillaries that reach to the highest layers of the stratum deliver nutrients to cells within the deepest levels of the skin through diffusion.[8] The different layers of epithelium are stratum spinous which is 5–10 cells thick. Desmosomes, or projecting spots, that area unit abounding in acanthus cells and enhance coupling between cuticle cells and provides resistance to physical stressors, span the animate thing gaps between spinous cells. The next layer is Stratum Granulomas It includes live cells, that area unit responsible for modifying and synthesizing additional keratinization-related proteins. The layer thickness is 1–3 cells. The last layer is Stomata Cornea is an eternal animate thing super molecule matrix covers the osteocytes, that are high in protein and low in lipid content (hydrophilic nature).[9]

Dermis:

It's robust connective tissues, hair follicles, and sweat glands, all of that are found within the dermis, that is found beneath the epidermis. A basement membrane firmly connects the dermis to the epidermis.[10]

Hypodermis:

The deeper body covering tissue (hypodermis), that is made of fat and animal tissue, isn't element of the skin. It performs is to produce the skin with blood vessels and nerves, similarly as connect it to the underlying bone and muscle. It created of elastin and loose connective tissue.[11]

III.ADVANTAGES OF NFIT: [12-17]

- The medicine is not over or under dosage.
- Use full for those who have a fear of needles.
- It offers a painless injection. It also has no side effects in terms of bleeding, bruising, or skin reaction.
- Provide rapid delivery and reproducibility comparable with needle & syrings.
- Patient compliance is improved, especially in long-term treatment.
- Self-administration is possible.
- Special types of disposals are not required.

- There is no chance for cross contamination from needlestick injuries.
- Both the depth and the dosage of the drug can be modified.
- Both viscous liquids and powdered vaccines can be administered.
- Due to the drug's delivery in dry powder form, it has better storage stability.

IV.DISADVANTAGES OF NFIT:

- The method is difficult and costly.[18]
- No single size fits for everyone.
- Training and maintenance of personnel are required.
- Start-up cost is high.
- It is not relevant for the intravenous route.[19]

V.DESIGN AND COMPONENT:

Fig 2: Components of Needle Free Injection Devices

Component 1: Injection device

It is made of plastic and has a medicated chamber. The device is kept sterile throughout. It is designed in such a way that self-administration is possible. It contains a plastic, sterilised, needle-free syringe. [20]

Component 2: Nozzle

The nozzle acts as the skin contact surface, and the medicine passes through this. The medicine is injected into the skin through an opening in the nozzle. The orifice is 100 m in diameter. Drug particles are discharged from the nozzle at a speed of 100 m/s and a depth of 2 mm. Because of this, the injection is painless; the patient feels a tap of gas, which feels like a finger flicking on their skin [21]

Component 3: Pressure source

It is crucial for forcing medication through the skin and into the bloodstream. A mechanical pressure source that uses a spring to store energy and a plunger to release it can be used to generate the required pressure.[22] It may also take the form of a pressure-storage technique that uses a gas cartridge for compressed gas. In portable devices, pressurised metal air cartridges are frequently provided for access. The most commonly used gases in equipment are nitrogen or carbon dioxide.[23]

VI. PRINCIPLE:

NFIT is based on the application of energy powerful enough to deliver a drug dose that has been premeasured and placed into specialised, one-of-a-kind "cassettes" that may be fitted with the system [24]. These forces can be produced in a variety of methods, such as high-pressure
fluids, including gases, electro-magnetic forces, shock waves, or any other type of energy that can give the medication motion.[25]

VII. MECHANISM:

The mechanism is based on the generation of force through an aperture at a high speed by utilising compressed gases like carbon dioxide or nitrogen.[26] An ultrafine stream of fluid that is delivered through the skin penetrates the skin and quickly delivers the vaccine to the skin, subcutaneous tissue, and intramuscular tissue.[27] An injection is given in three phases and takes less than one-third of a second to complete.[28]

Penetration of the skin at the peak pressure period, which lasts for around 0.025 seconds.
Dispersion phase, about 0.2 seconds.
The drop-off phase, which lasts for around 0.05 seconds.

VIII. TYPES OF NFIT:

1.Powder Injection: These comprise of a chamber with a solid drug substance loaded in it and a nozzle that fires drug particles into the skin using compressed gas as the power source. To cover the drug chamber, the injection features a few micron-thick diaphragm on either side of the chamber. Protein medications have a high potency and are appropriate for powder needle-free injection methods. [29]

Principle: The drug is administered through a pressured fluid contact with the skin in the powdered injection method. A drug cassette containing a predetermined amount of powder medicine is opened by compressed gas, allowing the medication to be administered to tissue.

Mechanism: The fundamental components of solid jet injectors are a drug compartment housing a particulate drug formulation, a nozzle to control the flow of particles, and a power supply made of compressed gas. Diaphragms on each side of the drug compartment, which are generally only a few microns thick, are used to seal it. When the actuation mechanism is activated, pressurised gas from a storage canister expands and presses up on the diaphragms, rupturing them one at a time. The drug particles are carried by the gas flow. The particles then emerge from a nozzle and strike the skin, where their motion causes them to penetrate the stratum corneum with microscopic holes.

Application: The delivery of DNA encoding for viral and bacterial antigens utilising coated gold microparticles has been researched for solid jet injectors. Studies on mice have demonstrated the induction of humoral and cell-mediated immune responses against rabies, hepatitis B, and influenza. Injecting DNA-coated gold microparticles and DNA-encased polymeric particles has also been shown to provide protection against cancers.

2.Liquid injections:

This injection creates a pressure that is high enough from a fluid in close contact with the skin to distribute liquid by puncturing the skin. These systems utilise nozzles with orifice sizes ranging from 150 to 300 m, gas or spring pistons, drug-loaded compartments, and gas or spring.

Principle: The fundamental idea behind this injection is that "if a fluid in close contact with the skin can produce a high enough pressure, then the liquid will punch a hole into the skin and be given to the tissues in and under the skin."

Mechanism: When the actuator is activated, the power supply pushes a piston into the drug-loaded chamber, quickly increasing pressure. This causes a liquid jet of medication solution travelling at a speed of between 100 and 200 m/s to emerge from the nozzle aperture. Through erosion, fracture, or other skin failure processes, the powerful stream of liquid's impact on the skin's surface causes a hole to develop in the skin. The powerful jet of liquid continues to press against the skin, deepening the hole. In the initial few hundred microseconds, a hole is thought to occur as a result of a combination of skin erosion and fracturing the liquid stream's velocity diminishes as its force increases deeper into the skin until it lacks the energy to complete the whole creation. This completes the initial injection phase, which involved a single path of skin puncture. The second phase, multidirectional jet dispersion from the end site of penetration. A few tens of microseconds after impact, the dimensions of the hole are determined. The liquid is distributed into the skin in a nearly spherical form by stagnation of the jet at the end of the opening.

Application: MUNJIs have been used in mass vaccination campaigns against illnesses including polio, cholera, hepatitis B, cholera, measles, and smallpox. Several proteins have been delivered using DCJIs. The majority of research has been done on erythropoietin and interferon administration, as well as the delivery of insulin and growth hormones. [30]

3. Depot Injection:

The projectile needle-free injection technique is another name for it. Technology has just recently made this step. The medication is created in this formulation as a long, thin, slender depot with sufficient strength to impart a driving force to a pointed tip. The pointed tip is made of a soluble inert substance like sugar. [31] The depot is pushed into the skin with enough force to penetrate both the skin and the fatty tissue. For the majority of proteins and antibodies, a depot with a typical diameter of 1 mm is sufficient. A punch with a sharp point may pierce the skin with 3 to 8 megapascals (MPa) of pressure. If the drug's liquid form is unstable and it has an effect in the milli gramme dosage range, this is especially beneficial and effective.[32]

Principle: A depot injection is an injectable type of a drug that releases gradually over time to allow for less frequent administration of a drug. They are intended to improve patients' consistency and adherence to their medication, particularly those who frequently forget to take it.[33]

Mechanism: Drugs can be altered such that they are slowly activated by the body or slowly absorbed by the body. Since the molecule is lipophilic and has functional groups added for delayed action, many are dissolved in an organic oil. A functional group like decanoate is an example of this. [34] The combination of an oil base and a change to reduce metabolic activation prevents medicine from being released completely. As a result, the duration of the activity may be 2-4 weeks or more.

Atypical antipsychotics are still favoured over typical antipsychotics because pharmacokinetics (the drug's absorption and activation) changes do not affect its side effect profile.[35]

Application: Many drugs, including many common and uncommon antipsychotics [36], as well as certain hormonal drugs and drugs for opioid use disorder, are accessible as depot injections. [37] Depot antipsychotic injections have been used to increase generally low adherence in people with diseases like schizophrenia.[38]

IX. CLASSIFICATION OF NFIT SYSTEM [39]

1.On the basis of working.
Spring systems.
Laser powered.
Energy propelled system
Lorentz force.
Gas propelled/air forced.
Shock wave

2.On the basis of type of load.
Liquid.
Powder
Projectile.

3.On the basis of mechanism of drug delivery.
Nano-patches.
Sandpaper assisted delivery.
Iontophoresis enabled
Micro-needles.

4.On the basis of site of delivery.
Intra dermal injectors
Intramuscular injectors.
Subcutaneous injectors.

X.RAW MATERIAL:

The materials used to make these devices, which come into close contact with the body, must be pharmacologically inactive. The exterior compartment or the body of the device should be made of synthetic materials that are lightweight, easy to shape, and synthetically generated.[40] These materials include thermoplastics and polycarbonates. Materials need to be able to withstand extreme temperatures. They've been heatedly sterilised. Systems for forced air injection come in a variety of sizes and designs. Fillers are added to the polymer to make it useful to mould. The use of fillers makes polymers stronger, lighter, and more rigid. Colorants are added to the plastic to change the overall look. [41]

XI. THE MANUFACTURING PROCESS:

Each needle-free injection system may be created using a variety of techniques.
The steps for making a needle-free injection system are as follows:

Moulding the pieces:

The manufacture of the individual plastic bits from plastic pellets is involved. The technique used for this is injection moulding. On an injection moulding process, plastic pellets are loaded into a large holding bin. To make them flowable, they are heated. The material is delivered via a screw that is hydraulically controlled. The plastic is forced into a nozzle as the screw turns, where it is subsequently injected into a mould. When the two metal parts of the mould are combined, they take on the form of the component. The plastic is forced into the mould, kept there for a predetermined period of time, and then given time to cool. The plastic inside thickens as it cools. The plastic component falls out of the mould onto a conveyor once the mould parts are separated. The process is then repeated as the mould closes once more. The plastic components are carefully examined when they are removed from the mould to make sure no seriously damaged components are used.[42]

Assembling and labelling:

Then, the parts are transferred to an assembly line. Various events take place in this production phase. Markings that display dosage levels and force measurements are applied by machines. These devices have been specifically tuned to produce exact printing on each page. Depending on the device's complexity, either humans or machines may put it together. To do this, attach any buttons and then place the different components into the main housing.[43]

Principal:

Injection devices are placed in cardboard or plastic boxes after being covered in sterile films. Pallets are then used to stack these boxes.[44]

Quality Control:

Checks for quality control are carried out at every stage of production. The plastic components are examined by line inspectors to ensure they meet predefined requirements. The primary test technique is visual examination, however measurement tools are also used to examine the dimensions, such as size and thickness. Callipers, microscopes, and laser micrometres are examples of tools that can be employed. Additionally, inspectors make sure that all the parts are contained in the final packaging and that the printing and labelling are accurate. The Food and Drug Administration tightly regulates the development of these devices due to potential safety concerns (FDA). Each producer is required to adhere to different production standards and requirements.[45]

XII. Types of NFIT drug delivery:

XIII. Spring loaded injector:

In order to inject the medicine into the underlying tissue, where it dissolves and is released into the blood stream, the spring-loaded injector employs a spring mechanism that is pulled back. For the subsequent administration, the active spring load needs to be manually repainted. Example includes Dermo jet®, Medi-jector®27.[46]

Battery powered:

Injector use of electricity as a fuel source. The dosing gadget is retractable using a tiny redrawn. It is utilised for medication administration via transdermal, intramuscular, and subcutaneous routes. Examples include applying liquids intravenously. (IDAL) ®-Intervet, Boxmeer28. [47]

Gas powered injector

It normally consists of three parts. This technique uses an air/gas cartridge that is connected to the gun through a tubing system to power the piston once the trigger is pulled. When the piston is released, a drug jet stream is created. It is appropriate for usage trans dermally, intramuscularly, or subcutaneously. Examples include Needle-Free-Felton, Biojector®, Pulse®, Lenexa, Ks. Agro-Jet®/MedJet®- Mit29 [48]

XIV. NEEDLE FREE INJECTION TECHNOLOGY: DRUG PREQUISTS

Shelf life:

The consistent power supply can provide non-prefilled gadgets the longer shelf life they need. The mechanics of the device must be such that they allow it to be triggered even after 2-3 years of storage under various storage conditions. The following considerations are necessary when discussing the prefilled NFIT system over its entire intended shelf life.

The final product must be sterile.

The predefined limit for endotoxins and foreign particles must be maintained to.

The leachable profile from the device's contact component into the formulation must not be excessive; rather, it must be acceptable.

Under no circumstances should the purity, composition, or concentration be diminished within the indicated shelf life.

The entire apparatus needs to be made of a material that is inert, cost-effective, mechanically strong, and stable.[49]

Viscosity:

Because the molecule is frequently bigger and has to be sufficiently concentrated to lay in a range of volume that may be injected comfortably, newer pharmaceutical preparations are being developed. The traditional needle syringe system makes it difficult to deliver the various preparations because the hypodermic needle acts as a pipe, decreasing pressure along the length of the pipe (in this case, the needle). To put it another way, the user must exert more pressure on the plunger when injecting a viscous fluid than when injecting a no viscous one. Additionally, the additional effort needed increases along with the viscosity. Since they don't require any hollow needles, needle-free devices have been demonstrated to be effective in delivering a variety of formulations with varied viscosities.[50]

XV. Marketed Product:[51]

Marketed item

There are a number of liquid jet injection technologies on the market, such as Merck Serono's Saizen Cool and Ferring's Zomajet 2 Vision. All of the human growth hormone products are Click and Tev Tropin Tjet from Teva. Additionally offered is Zogenix's Sumavel DosePro, an injectable of sumatriptan used to treat migraines. However, these liquid jet injection devices are more expensive than the majority of auto-injectors and pen-injectors, which also have the benefit of being simple for patients to use at home. When compared to other delivery methods, the main advantages of eliminating a needle and convenience of use of a liquid jet injector do not exceed the overall cost of the product.

Table:1 Marketed products of NFI

Technology/product name	Company name	Description
Implaject	Caretek Medical	Simple, portable needle-free injection tool. may be set up to use replaceable cartridges with it.
Powder Ject	Powder Med	It uses a dry formulation to gently administer DNA vaccinations to the skin.
Zoma-jet 2 Vision	Antares Pharma	The Medi-jector Vision model that Ferring has obtained a licence for, in order to administer Zomacton, its human growth hormone product for sale in Europe.
Valeo (MJ8)	Antares Pharma	newest pen-style, spring-powered gadget. designed to be used with medicines that are stored in cartridge containers as opposed to vials.
Injex 30	Injex (HNS International	0.05–0.3ml disposable ampoules are delivered by a spring-powered portable device. concentrating on insulin administration.
Med-E- jet	Evans enterprise	Needle free injection
Crossject	Crossject	NFI that has been prefilled and is disposable. uses a chemical process to produce propellant when administered

XVI.

XVII.

XVIII. **APPICATIONS:** [52-54]

- The ideal choice for needleless delivery is insulin because it needs to be taken numerous times a day.
- A local anaesthetic called lidocaine hydrochloride can be administered without using a needle.
- Needles-free injection can be used to provide heparin (an anticoagulant), erythropoietin, lidocaine hydrochloride (a local anaesthetic), and several vaccinations.
- Patients who are minors Children become particularly difficult dental patients because they are so terrified and don't comprehend why the procedure is necessary.
- Patient adults Many folks are terrified of both the discomfort associated with getting dental work done and syringes with needles. The "needle-free syringe" will help to solve this issue.
- Haemophilia- The first needle-free reconstitution device with a prefilled diluent syringe was developed for haemophilia, a hereditary condition.
- Hyperhidrosis-This skin condition causes excessive sweating, which makes the palms and other body parts damp.

XIX. CONCLUSION:

The first way is to use a needle-free injection system, which eliminates the need for needles. Injectors are now being used in many hospitals and homes to help people who are afraid of needles. We argue that the needle free injection system will be an effective alternative to traditional injections for those who have difficulties with needles. Medical procedures have been revolutionized with the invention of the needle-free injection system. The main point of this invention is to create as much less pain as possible for patients by removing needles from the equation. This new NFIT is an innovative idea that will make medical procedures more comfortable for all parties involved in the process. In conclusion, needle free injection systems are beneficial and have a lot of potential. This system is more than just a new way to give injections. It is a game changer that will change the face of healthcare forever.

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