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Review on Needle Free Injection Technology

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A B S T R A C T

Introduction: Needle-free injection technology (NFIT), its advantages, and the different devices and variants available. It highlights the potential of NFIT for painless and effective drug delivery and its use in mass vaccination campaigns.

Methods: The primary factors that need to be considered to provide a stable, safe, and effective dose by NFIT. It also explains the classification of NFIT devices based on their working, type of load, mechanism of drug delivery, and site of delivery.

Results: The additional benefit of NFIT technology, which is the ability to administer highly viscous medicated formulations that cannot be administered by conventional needle and syringe systems. It also highlights some of the commercially available variants of NFIT devices, such as Bioject®, ZetaJetTM, and Vitajet.

Conclusion: The advantages and potential of NFIT for painless and effective drug delivery, particularly in mass vaccination campaigns and the developing world. It emphasizes the need for further research and development in this field to improve the stability, safety, and efficacy of NFIT devices.

Key Words: Needle Free Injections, Vaccination, Pain free Injections,

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INTRODUCTION

In the past few years, needle free injection technologies (NFIT) have become more common and offer a number of advantages as a means of overcoming challenges associated with injections using needles. These technologies are designed to deliver liquid formulas as well as solid particle dosage forms of medications and vaccines.

NFIT are innovative techniques for transferring medication directly through the skin without piercing or otherwise compromising its health. These tools can also be used to inject medications into the muscle. NFIT has shown promising results in mass immunization and vaccination programs. Since they do not use traditional needles, these devices are almost completely painless.

Needle-free systems were first described by Marshall Lockhart in 1936 in his patent jet injection. Then in the early 1940's Higson and others developed high pressure "guns" using a fine jet of liquid to pierce the skin and deposit the drug in underlying tissue.[1,2]

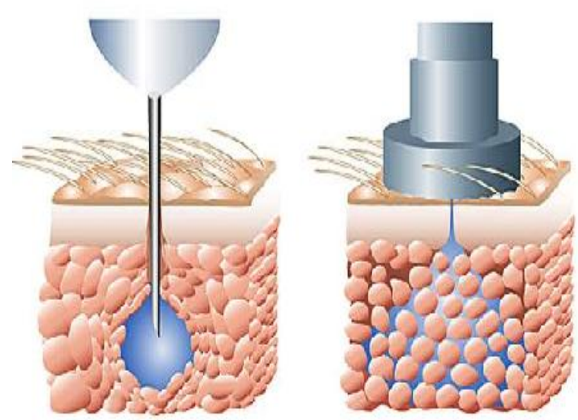

Figure1: Needle-free injection system [3]

Components of Nfit

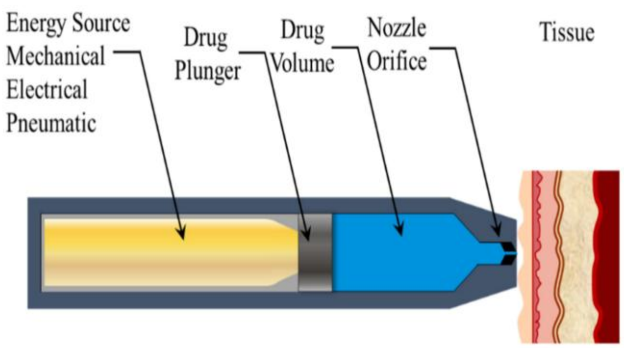

Figure2: Components of a needle free injection device[4]

Needle-free injection devises consists of three (3) main components:

1. **Injection device:** It is built with a medication compartment and allows for self-administration. The gadget is composed of plastic. Sterility is maintained throughout the device. It has a sterilized needle-free syringe which is made of plastic.[5]
2. **Nozzle:** The nozzle has an orifice through which the drug enters skin when injected. The diameter of orifice typically is 100 µm[6]
3. **Pressure/Energy source:** It is important for delivering a drug forcefully into the systemic circulation via the skin. The pressure source can be a mechanical method which stores energy in a spring and is released by pushing a plunger to provide the necessary pressure. The most popular gases used in devices are carbon dioxide or nitrogen.[7]

General Advantages

- Prevent skin puncture hazards and its destruction; also, does not cause problem of bleeding or bruisingand minimal skin response.[8]
- No under- or overdosing condition of the drugs[9].
- Useful in case of patients with needle phobia.
- It delivers pain-free injection. Prevents skin puncture hazards and its destruction; also does not cause problem of bleeding or bruising and minimal skin response10].
- Improved patient compliance especially in chronic administration of drugs[11]
- No need to visit hospitals / experts for injections, i,e., self-administration is feasible.
- No specific disposal requirements.
- No risk of cross contamination from needle-stick injury[12]
- Amount of medicine delivered and the depth can be adjusted.
- Vaccines can be delivered in powdered form as well as viscous liquids[13]
- Better drug stability during storage as it is delivered in dry powder form
- Bioequivalence has been demonstrated enabling the development of generic drug protein.[14]

Disadvantage

- High start-up cost.
- No one size-fits all system.
- Greater complexity.
- Cannot be used for Intravenous route.
- Infrastructure for exhaustible gas systems.
- Higher requirement for training and maintenance.[14,15]

Types of Needle Free Injection Systems

Needle-free injection drug delivery systems refer to a range of technologies that enable drug administration without using traditional hypodermic needles:[8]

1. Powder injections[17]
2. Liquid injections
3. Depot or Projectile Injection.

Some of the other types:

Jet injectors: These devices use high-pressure streams of liquid to deliver drugs through the skin. Examples include Biojector 2000 and Injex 30[10]

Nanoparticle injectors: These systems use nanoparticles as carriers to deliver drugs into the skin. Examples include liposomes and polymeric nanoparticles[20]

Microstructured systems: These systems utilize microstructures or microneedles to pierce the skin and deliver drugs into the underlying tissue. Examples include microneedle patches such as the Zosano Pharma's Microneedle Array Patch[21]

Shock wave-based injectors: These systems use shock waves to create temporary pores in the skin, allowing drugs to pass through. An example of a shock wave-based injector is the Lancer Rx's Contour[18]

Powder Injection

Powder jet injectors deliver vaccines or drugs in dry powdered form into superficial layers of skin. The terms biolistic injectors and gene guns have also been commonly used for these injectors, with the latter term used exclusively for DNA delivery. These injections consist of a chamber filled with solid drug content and a nozzle for firing drug particles into the skin by utilizing the power source which typically is compressed gas. The powders used in these systems require specific properties and specific size to ensure their stability and proper dispersion into the tissue.[22]

In order to create particles with a sufficient density and accelerate them to a sufficient speed to pierce the skin, the basic idea uses the non-reactive gas helium. [23]to reach dose levels that are therapeutic.

The particles should be carried or coated using the vector or medium.

Principle

Principle involved in powdered injection system is, the medications are delivered by pressurized contact of fluids with the skin. A known quantity of powder medication is put in a drug cassette which is opened by the compressed gas and thus the medication is delivered to tissue.

Mechanism

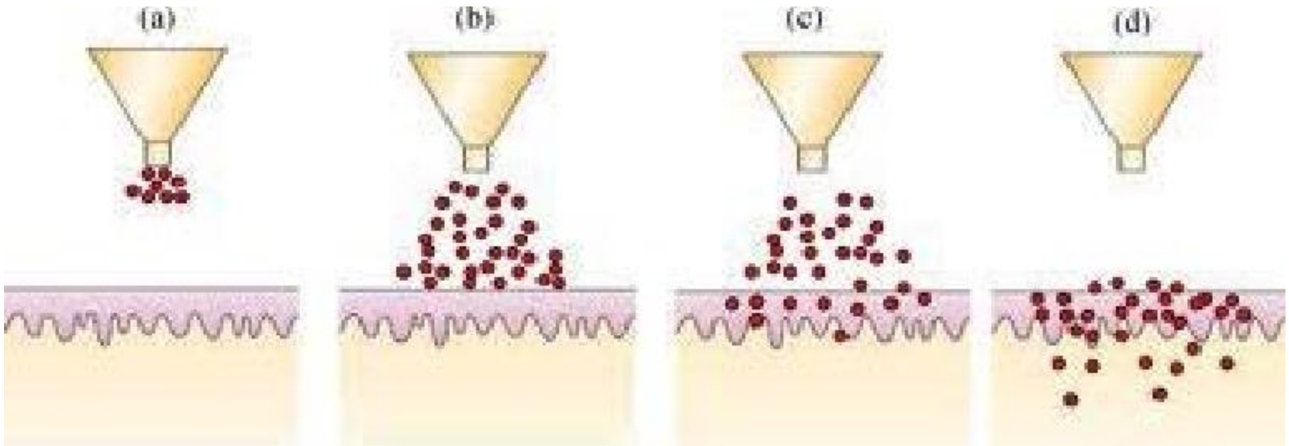

Figure 3: Mechanism of powder injection. Schematic of drug delivery using powder injector (a) ejection of particles from nozzle, (b) impact of particles on skin surface, (c)penetration of particles across stratum corneum, (d) completion of delivery. Particles which penetrate the skin are mostly distributed in stratum corneum and viable epidermis.[22,8]

Basic design of solid jet injectors includes compressed gas as the power source, a drug compartment containing particulate drug formulation, and a nozzle to direct the flow of particles. The drug compartment is closed with diaphragms on either side, which are typically few microns thick. Upon triggering the actuation mechanism, compressed gas from a storage canister expands and pushes against the diaphragms, sequentially rupturing them. The flow of gas carries the drug particles with it. The particles then exit through a nozzle and impinge on skin & upon impacting on the skin; particles puncture micron- sized holes into stratum corneum by virtue of their momentum. (Figure3)[24]

The fundamental idea behind this injection is the creation of high enough pressure by a fluid in close proximity to the skin in order to distribute liquid by puncturing the skin. These systems employ pistons, gas or springs, drug-loaded compartments and nozzles with orifice sizes ranging from 150 to 300 micrometer.[25]

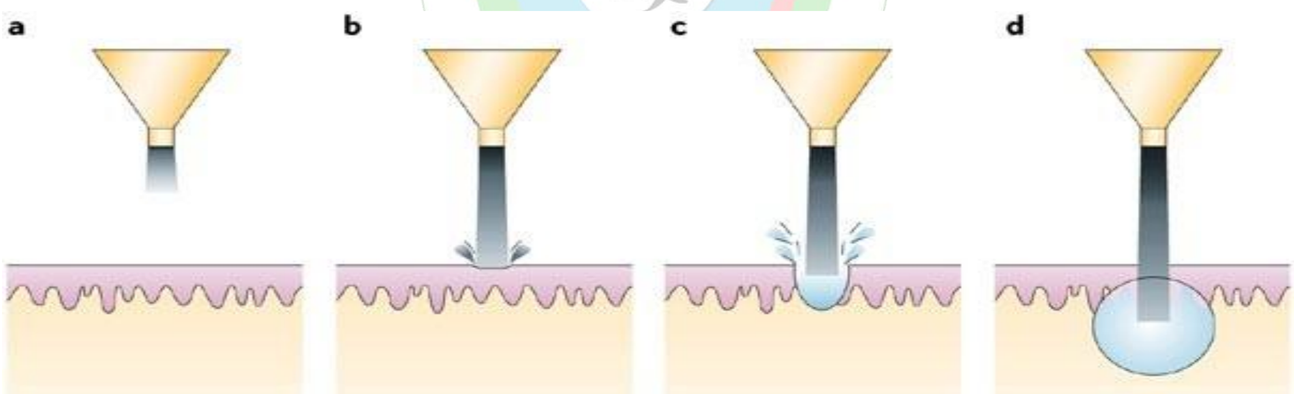

Figure 2: Schematic depiction of the jet injection process.[8]

Liquid Injections

Liquid jet injections employ a high-speed jet to puncture the skin and deliver drugs without the use of a needle. Since then, two main classes of liquid jet injectors have been developed. These are single-dose jet injectors, known as DCJIs (disposable cartridge jet injectors) and

MUNJIs (multi-use-nozzle jet injectors) These systems use gas or spring, pistons,drug loaded compartments and nozzles. Typically, the nozzle has an orifice size of about 150 to 300µm[26]

Mechanism of Working

The force produced by a pressurized gas (typically air, CO2, or nitrogen) is used in needle-free injection technology to push the vaccine through a small orifice at a fast speed. When a vaccine is given topically, a thin stream of fluid permeates the skin and quickly delivers the medication to the epidermis, subcutaneous tissue, and intramuscular tissue. Injection event requires less than 0.5 seconds.

Principle

The basic principle of this injection is "if a high enough pressure can be generated by a fluid in intimate contact with the skin, then the liquid will punch a hole into the skin and be delivered into the tissues in and under the skin"[27]

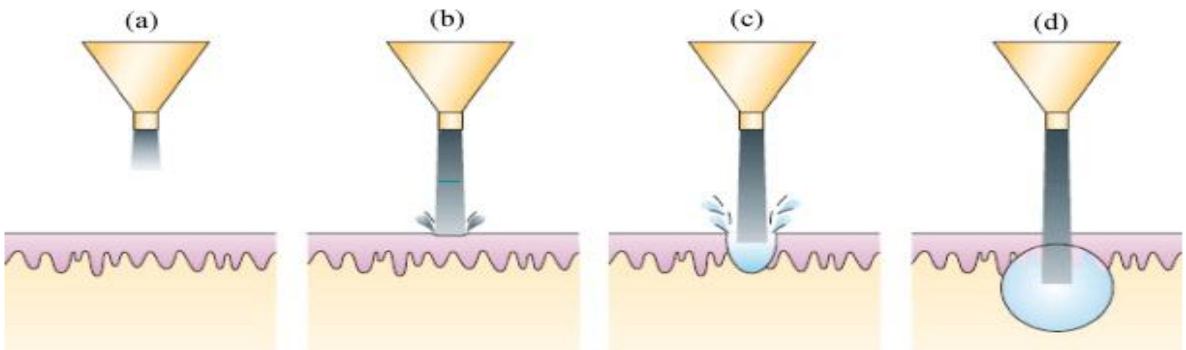

Figure 4: Mechanism of liquid injection.Schematic of drug delivery using liquid jet injector: (a) formation of liquid jet, (b) initiation of hole formation due to impact of jet on skin surface, (c) development of hole inside skin with progress of injection, (d) deposition of drug at the end of hole in a near spherical or hemispherical pattern (spherical pattern shown)[28]

On triggering the actuator, the power source pushes the piston which impacts the drug-loaded compartment, which leads to a quick increase in pressure. This pushes the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200m/s. A schematic representation of injection process is shown in Fig. 4

The effect of the forceful stream of liquid on the skin surface starts the formation of a hole in the skin through erosion, fracture, or other skin failure mechanisms. Further impingement of the forceful stream of liquid increases the depth of the hole in the skin. The formation of a hole is believed to be due to a combination of skin erosion and fracture and is completed during the first few hundred microseconds. As the forcefulness of the liquid stream progresses deeper in the skin, velocity decreases until it does not have sufficient energy to continue whole formation. This completes the first phase of injection i.e., unidirectional skin puncture and followed by the second phase, multidirectional jet dispersion from the end point of penetration. The dimensions of the hole are established very early in the process (a few tens of microseconds) from the time of impact. Stagnation of the jet at the end of the hole disperses the liquid into the skin in a near-spherical shape.

Advantages of liquid injections

1. A small volume of material, shot through the skin as drug, is in powder form instead of liquid form, hence injection is painless.
2. The therapeutic agent will be more stable and there is no need of cold storage.
3. The sustained release effect or drug performance can be achieved by using bio erodible carriers, slowly dissolving excipients specific, less soluble salts or dissolution aids.
4. Protein drugs are very potent, and suitable for powder needle free injection systems[29]

Application of liquid injections

MUNJIs have been used for mass immunization programs for diseases including measles, smallpox, cholera, hepatitis B, influenza, and polio.

DCJIs have been used for delivery of several proteins. Most work has been done on delivery of insulin and growth hormones, while erythropoietin and interferon have also been delivered.[22]

Depot Injections

Depot Injection: Also known as projectile needle free injection technology. It is a very recent advancement of the technology. In this the drug is formulated into a slender, long, thin depot having enough robustness to transmit a driving force to a pointed tip, the tip is formed of a soluble inert material like sugar. The depot is driven into the skin with a sufficient force to penetrate the skin and fatty tissue. A typical depot is about 1mm in diameter which is adequate for most proteins and antibodies. The pressure of 3-8 mega pascals (MPa) is enough to puncture the skin with a sharp tipped punch. This is particularly useful and advantageous for drugs that are affective in the milligram dose range, and if, liquid forms of the drugs are unstable.[30]

1. Spring loaded injector- The spring loaded injector uses a spring mechanism which is drawn back to push the drug into the underlying tissue where the drug dissolves and is released into the blood stream. The activated spring load must be redrawn manually for the next administration. Examples includesDermojet®, Medi-jector® [31].
2. Battery powered injector—Use of electricity as source of energy. It consists of a small rechargeable battery pack to retract the dosing device. The dosing device has an electric piston which is automatically redrawn after dosing. It is used for subcutaneous, intramuscular or transdermal delivery of drug. Examples include intradermal application of liquids (IDAL) ®-Intervet, Boxmeer[32].
3. Gas powered injector- It is typically made of three components. This system consists of an air/gas cartridge which is attached to the gun through a tubing system that delivers power to the piston after trigger actuation; it releases the piston and creates jet stream of drug. It is suitable for subcutaneous, intramuscular or transdermal use. Examples include Needle-Free-Felton, Biojector®, Pulse®, Lenexa, Ks. Agro-Jet®/MedJet®- Mit[33, 34]

Applications of Needle Free Injections:

1. Vaccine delivery: Needle-free injection technologies have shown promising results in delivering vaccines to patients. Studies have demonstrated that needle-free injection systems can induce immune responses comparable to traditional needle-based delivery methods [16]
2. Insulin delivery: Needle-free injection systems have been investigated as an alternative to traditional needle-based insulin delivery. Studies have shown that needle-free injection systems can provide comparable glycemic control to traditional methods [35]
3. Pain management: Needle-free injection systems can provide an alternative method of delivering local anesthetics and other pain management drugs without the use of needles[36]
4. Treatment of allergies: Needle-free injection systems have been investigated for the treatment of allergies, including the delivery of allergy immunotherapy [37]
5. Cancer therapy: Needle-free injection systems have been studied as a method of delivering cancer therapies such as chemotherapy and targeted therapies 38]
6. Delivery of biologics: Needle-free injection systems can be used to deliver biologic drugs, such as monoclonal antibodies, with comparable efficacy to traditional needle-based delivery [39]
7. Pain-free blood glucose monitoring: Needle-free injection systems have been investigated for pain-free blood glucose monitoring in patients with diabetes [40]
8. Hormone therapy: Needle-free injection systems have been studied as an alternative method of delivering hormone therapy for conditions such as osteoporosis and hypogonadism [41]
9. Delivery of gene therapies: Needle-free injection systems have been studied as a method of delivering gene therapies, including DNA vaccines [19]
10. Delivery of micronutrients: Needle-free injection systems can be used to deliver micronutrients such as vitamins and minerals to patients, including those with malabsorption disorders [42]

Advances In Needle Free Injection Technology

1. Biojector

It is the only system for intramuscular use which is approved by FDA. Cross contamination is avoided as it consists of single use syringes for individual injections. In situations involving greater risk factors, such as giving medication to patients who are HIV or hepatitis C positive, this method has proven to be secure and effective. [43]

Figure 5: Biojector[21]

2. Vitajet3

The device consists of disposable nozzles which are replaceable once a week. This device is used for delivery of insulin subcutaneously. It received FDA approval for marketing in 1996.[44]

Figure 6: Vitajet3

3. Zeta Jet TM

It is a compact, spring-powered, needle-free injection device. It is intended to deliver vaccines and injectable medications either subcutaneously or intramuscularly. The Zetajet™ uses jet force to propel a finely dispersed stream of injectable medication into the subcutaneous or intramuscular tissue without the use of a needle.[8]

Figure 8: Zetajet[45]

4. Cool click

This system is developed for administration of Saizen recombinant human growth hormone via the subcutaneous route. The system was approved by FDA in June 2000[11]

Figure 9: Cool click [46]

5. Serojet

The Serojet device is tailored from Vitajet technology. The device is designed for delivering Serostim recombinant human growth hormone administered subcutaneously. This is used for treatment of HIV associated wasting in adults and was approved by FDA in March 2001 for marketing.[8]

Figure 10: Serojet

6. Intraject technology

The device looks like fountain pen which is pre-filled and disposable. The device is suitable for liquid protein formulation. The drug delivery occurs by pushing actuator by using compressed nitrogen in less than 60 milliseconds.[8]

7. Biovalve's Mini-Ject technology

Device is suitable for delivering large proteins, fragile antibodies, and vaccines. Used for intradermal, subcutaneous, and intramuscular administration.

Figure 11: Biovalves Mini-Jet technology

8. Madajet

The injector commonly used in dentistry. It works by using pneumatic pressure to discharge local anesthetic [45]

9. Mhi-500

This device is used for subcutaneous administration of insulin. The system was approved by FDA in 1996 and for sale throughout Europe. The device creates a fine jet of insulin through the nozzle penetrating skin tissues of the subcutaneous layer[28, 47]

10. Injex needle free injections for infiltration anesthesia.

This device has an injection ampoule having an orifice of 0.18 mm. From this orifice, the drug is fired under dosed pressure into the submucosa. The system offers administration of local anesthesia. The ampoule must be placed on the attached gingiva at an angle of 90° directly above the tooth to be anaesthetized. The local anesthetic volume that can be administered is about 0.3 mL [45]

CONCLUSION

Needle phobia and accidental needle-stick injuries have not only worsened patient compliance, but even unnecessary problems have surfaced. Needle free technology are capable of delivering a wide spectrum of medicinal formulations into the body with the same bioequivalence as that which could have been achieved by drug administration by a two-piece syringe system, without inflating unnecessary pain to the patients.

These gadgets are very simple to use, do not need any special handling or guidance, and are simple to discard of. These tools are appropriate for delivering medications to some of the body's most delicate organs, such as the eye. Intramuscular, intramuscular, and intradermal shots can be given with efficiency.

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