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A REVIEW ON NEEDLE FREE INJECTIONS

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Abstract:

Needle free injection system introduces the various medicines into patients without piercing the skin with conventional needle. Needle free injections are novel ways to introduce various medicines into patients without piercing the skin with conventional needle. It results in less pain and is strongly preferred by the patients. It is very fast and rapid injection compared with conventional needles and no needle is disposable issues. It also can inject such as powder injection, liquid injection, and projectile injections. Today they are steadily developing technology that promises to make the administration of medicine more efficient and less painful.

Keywords-*Needle free injections, Needle less technologies, Drug delivery, Jet injections,Local drug delivery.*

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INTRODUCTION:

At present situation, many researches are working to develop technology that promises to make the administration of medicine more efficient and less painful (1). There are a variety of problems associated with hypodermic needles used in injections. Diseases are available in reusable and disposable forms, for home or physicians office use, and also in versions for multiple patients and institutional uses. These include relatively high cost of needles, lack of reusable i.e. needle syringe should be sterilized additionally; many people have a fear of needles or needles or needle-phobia, which causes them to avoid treatment (2). In general, needle free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. This creates an ultra fine stream of high pressure fluid that penetrates the skin without the use of needle (3). Needle free devices are taken to form of power spray, edible products, inhalers and skin patches. These devices are available in reusable and disposable forms for home and physicians office use, and also in versions for multiple patients and the institutional use (4).

History:

The first syringes were the first developed by French surgeon Charles Gabriel Pravaz, in 1853, hypodermic there is minor development in syringes in technology has remained unchanged for last 150 years. Needle free systems were first described by Marshall Lockhart in 1936 in his patent jet injection. Then in the early 1940's Hingson and others developed high pressure "guns" using a fine jet of liquid to pierce the skin and deposit the drug in the underlying tissue (5).

Advantages:

- Useful in case of patients with needle phobia.
- Prevent skin puncture hazards and its destructions; also does not cause problem of bleeding or bruising and minimal skin response (6).
- Bio equivalence has been demonstrated enabling the development of generic drug proteins.
- No need to visit hospitals/ experts for injections i.e. self administration is feasible.
- Vaccines can be delivered in powdered from as well as viscous liquids (7).
- Avoid problems of reconstitution and any effect of shearing (8).
- Elimination of needle phobia
- Improved patient compliances especially in chronic administration of drug (9).

Disadvantages:

- Need for personnel training and maintenance (10).
- Method is complex and expensive (11).
- It is not applicable for intravenous route.
- The high pressure delivery of drug can be damage fragile molecules beneath the skin layer.
- Higher start up cost.

Components of the needle free injection systems:

Devices may vary in design depending upon the drug which they are used.

❖ **1.Injection device:**

It is made with a drug chamber and can be used for self-administration. The gadget is composed of plastic. The equipment is always kept sterile.

It comes with a plastic needle-free syringe that has been disinfected. It is made with a drug chamber and can be used for self-administration. The gadget is composed of plastic. The equipment is always kept sterile.

It comes with a plastic needle-free syringe that has been disinfected.

❖ **2.Nozzle:**

The medicine travels through the nozzle, which also acts as the skin-contact surface. When the medicine is applied, it enters the skin through an opening in the nozzle injected. Usually, the orifice's diameter is 100 m. Drug particles are fired from the nozzle at a typical rate of 2 mm of depth at 100 m/s. The most typical0.127mm orifice size, equivalent to a 25-guage needle. Consequently, this injection is harmless; User experiences what feels like a tap of gasoline on the skin. Rubbing your skin with your finger (12).

❖ **3. Pressure source:**
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. It is crucial for forcing a medication through the skin and into the bloodstream. Carbon dioxide and nitrogen are the most often used gases in equipment. Then, as energy storage components, many products on the market use either mechanical or stored pressure. The mechanical method uses a spring to store energy that is then released by moving a plunger to provide the required pressure (13).

Structure of human skin:
Since pharmaceuticals are delivered to the skin using needle-free injection devices, understanding the anatomy of the skin is crucial for efficient drug **(**14**).**
Administration.
In general, the human skin has two layers
1. Dermis
2. Epidermis

1. The Dermis
Dermal layer It is supported by an integrated system of amorphous, filamentous, and fibrous connective tissue that allows for the entry of nerves, circulatory networks, appendages, fibroblasts, and mast cells that are produced by stimuli. Its thickness varies between 2000 and 3000 m. Collagen, which comprises 70% of the dry weight of the skin, is the primary element of the dermis (15).

Sub-cutaneous (Connective Tissue)
Although it contains blood and lymphatic arteries, sweat gland secretary pores, and cutaneous nerves, the subcutaneous tissue, also known as the hypodermis, is not actually thought of as a true component of the organised connective tissue. While adipose tissue may act as a drug store, most researchers believe that drugs that penetrate the skin enter the circulatory system before they reach the hypodermis **(**16**).**

2. The epidermis:
This is a stratified squamous epithelium layer i.e. are composed primarily of two types of cells: keratinocytes and dendrite cells. The Epidermis layers are harbouring a number of other cells such as melanocytes, Langerhans cells and Merkel cells. But the keratinocytes cells types comprises the majority of the cells by far. The layers of epithelium are,

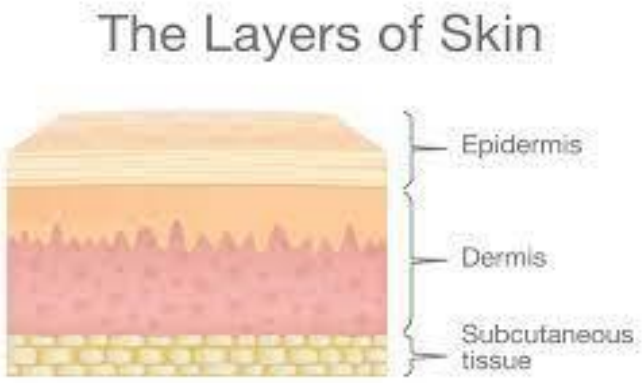

Figure 1: The layers of skin.

Stratum Corneum:
A continuous extracellular lipid matrix surrounds the corneocytes, which are hydrophilic in nature and high in protein but low in lipid content (17).

Stratum granulosum:
It contains live cells that are in charge of continuing to synthesise and alter the keratinization-related proteins. It has a thickness of 1-3 cellular layers (18).

Mechanism of Needle free injections:
By forcing the drug through an opening at a very high speed using compressed gas (such carbon dioxide or nitrogen), the method creates force. A stream of fluid that is so thin that can pass through the epidermal layers while a medicine is being administered through a device swiftly enters the systemic circulation. An injection is given in three phases and takes less than one-third of a second to complete.

Stage 1 is the peak pressure phase, which is utilized to penetrate to the skin at the best pressure (0.025 seconds).
Stage 2: the dispersion or delivery phase (less than 0.2 seconds).
Stage 3: the drop-off period (0.05 seconds).
Each time the vaccine is administered; this pressure profile ensures that the proper tissue depth is reached for each animal. The method for needle-free injections enhances the medication's distribution throughout the tissue. As the fluid stream forces its way through the tissue, it follows the path of least resistance, resulting in a widely spread, spider-web-like dispersion of the drug.

Types of needle free injections:

1. **Powder injections:**
   These are made up of a chamber with a solid drug substance loaded in it and a nozzle that uses compressed gas as its power source to fire drug particles into the skin. Since only a small amount of the substance is injected into the skin as a drug rather than a liquid—the injection is painless. To cover the drug chamber, the injection has a few micron-thick diaphragms on either side of the chamber (19).Utilizing bioerodible carriers, slowly dissolving excipient-specific, less soluble salts, or dissolution aids can produce the sustained release effect or improve medication performance. Protein medications can be used in powder-free injectable systems because of their high potency (20).

Mechanism of powder injections
(a) The nozzle emits both a gas stream and particles.
(b) As the injection progresses, particles impinge on the skin's surface, causing a hole to grow in the skin.
(c) Drug particles enter the stratum corneum through the hole's end and are deposited there in a spherical arrangement.
(d) Drug particles spread evenly throughout the stratum corneum and the viable epidermis after penetrating the skin (21). An electric gas gun is used to inject powder. By using an accelerating piston that accelerates and carries particles along with it, it produces the necessary particle velocity. Particles leave piston surface by means of a de acceleration mechanism which slows down the piston. Particles that operate on the target tissue area are ejected as a result.

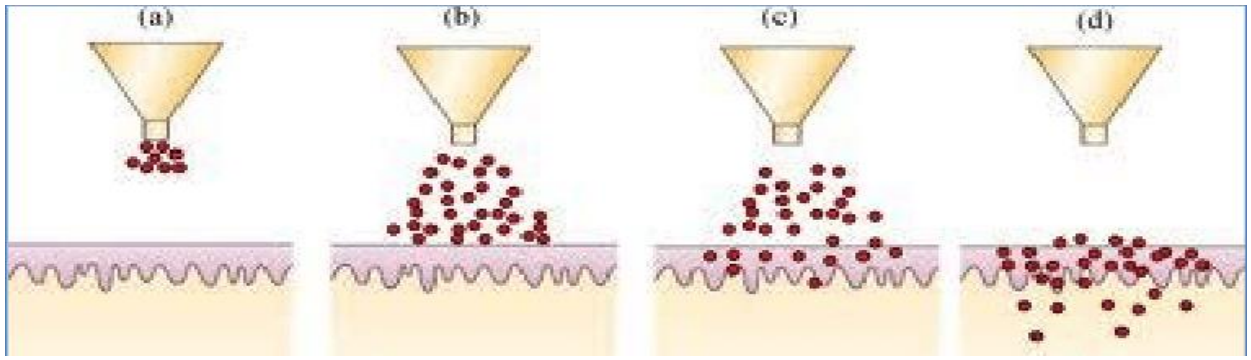

Figure 2: Mechanism of powder injection

Characteristics of powder injections:

- Because particle size affects penetration into the stratum Corneum, it must stay constant during use and storage **(**22**)**
- A full drug or a formulation including a drug and excipient for stabilization or dilution may be used as powder in an injection. Drug and other excipient must therefore be compatible with one another (22).
- The drug particles must diffuse properly in the skin for them to have the desired effects in the body after entering systemic circulation (22).
- The particles must be durable enough to withstand both the device's highly intense gas jet and a ballistic collision with the skin. The particles must be powerful because they hit the skin quickly. Particle speeds have been measured up to 900 meters per second, however 400 to 600 meters per second is more frequent (22).
- The powders need to have mean diameters higher than 20 m and particle densities of around 1g/cc for rapid skin penetration (22).

  The powders are processed by compression, milling, sieving, and more scalable techniques like spray drying, freeze drying, fluid bed drying, spray coating of seed particles, solution filling and drying of pre-formed hydro gel beads, and emulsion techniques to create erodible micro particles in these injection systems.

Advantages of powder injections:

- Utilizing bioerodible carriers, slowly dissolving excipient-specific, less soluble salts, or dissolution aids can produce the sustained release effect or improve medication performance.
- Since only a small amount of the substance is injected into the skin as a drug—rather than a liquid—the injection is painless.
- There won't be a requirement for cold storage because the therapeutic substance will be more stable (23).
- Protein medications can be used in powder-free injectable systems because of their high potency.

1. **Liquid injections:**

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 utilize nozzles with orifice sizes ranging from 150 to 300 m, gas or spring pistons, drug-loaded compartments, and gas or spring (24).

Mechanism of liquid injection:

- The hole in the skin gets deeper as the jet continues to impinge. Some of the liquid may splash back towards the injector if the volumetric rate of hole formation is lower than the volumetric rate of the jet impinging the skin.
- A deeper skin hole that delays the incoming jet is the source of the liquid building up in the hole. Consequently, a hole's ability to grow is prevented. In the first few tens of microseconds after impact, the dimensions of the hole are determined. The liquid is distributed into the skin in a nearly spherical shape by stagnation of the jet at the end of the opening (25).

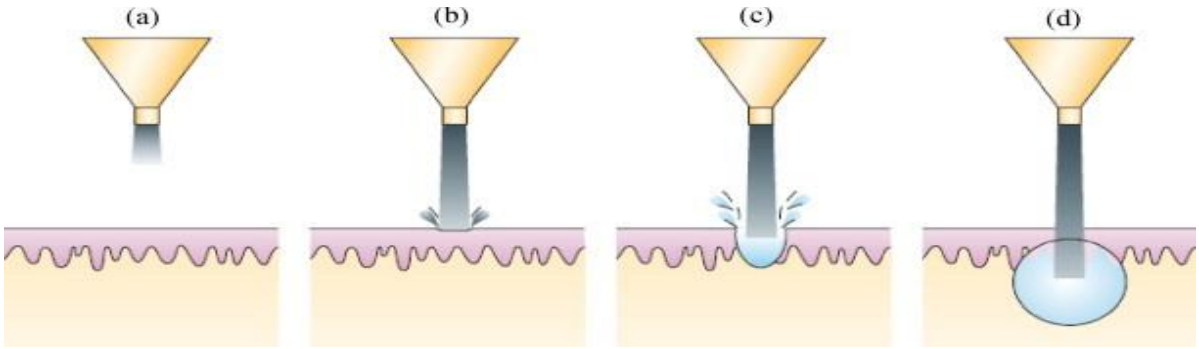

Figure 3: Mechanism of liquid injections

3. Depot or projectile injections:
These are made to deliver medication into muscles. They build up a pharmacological
Reserve in the muscles that is constantly delivered for the desired amount of time (26).

Types of injection methods:

- Battery powdered jet injector **(**27**).**
- Gas powdered jet injector (27).
- Spring load jet injector (27).

Battery powdered jet injector:
The retractable dosage mechanism for this method is powered by a tiny rechargeable battery pack. After dosing, the dosing device's electric piston is automatically redrawn. This is suitable for ongoing use. This kind of injector is comparable to a hand drill that runs on batteries. used to deliver drugs via transdermal, intramuscular, or subcutaneous routes depending on the prescribed route. Intra Dermal Application of Liquids (IDAL) ®- Intervet and Boxmeer are two examples (28).

Gas powdered jet injections:
This technique uses an air/gas cartridge that is connected to the gun via a tubing system to power the piston once the trigger is pulled. When the piston is released, a drug jet stream is created. It can be used transdermally, intramuscularly, or subcutaneously. Examples include Biojector® and Pulse®. Needle-Free - Felton - Lenexa, Kansas Agro-Jet – Med jet - Montreal - Quebec – Canada (29).

Spring load jet injector
Using a spring mechanism that is drawn back, this technique operates. By pulling the trigger, the spring is released, creating a jet stream of medication for subcutaneous, intramuscular, or transdermal drug delivery. For the subsequent administration, the activated spring load must be manually repainted. Examples include Medi-jector and Dermojet (29).

Classification of needle free injection technology:
1. On the basis of working
    - Spring systems
    - Laser-powdered
    - Energy propelled systems
    - Lorentz force
    - Gas propelled/Air forced
    - Shock waves
2. On the basis of the type of load
    - Liquid
    - Powder
    - Projectile/Depot

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

4. On the basis of site of delivery
    - Intra dermal injector
    - Intra muscular injectors
    - Sub cutaneous injectors

1. On the basis of working

- **Spring system:**

It has been demonstrated that using springs to store energy is a very efficient way to power NFIT devices. Energy storage and further transmission via a spring is one of the simplest and most straightforward NFIT applications. To prevent the spring from taking a "set" over time and degrading the device's function, the design of the spring must adhere to standard procedures, and the storage conditions must be straightforward. The fundamental problem with the spring's design is that, in accordance with Hook's rule, the force the spring provides will decrease according to the length of time the load has been applied. Simply said, during an injection with a spring-assisted NFIT, the pressure must gradually drop (29).

- **Laser powdered:**

Professor Jack Yoh and his team at the Department of Mechanical and Aerospace Engineering at Seol National University in South Korea have created a more recent NFIT technique that uses a laser-based device to inject small drug jets into the skin.

The technique drives a very fine and precise stream of drug or medication with just the correct amount of force using an erbium-doped yttrium garnet laser (the one used in the treatment of laser resurfacing of the skin). An adapter that holds the medicine to be delivered is built within the laser. The gadget also has a chamber for the water that powers the medication, but the arrangement is made in such a way that the membrane separates the drug from the water that powers it.

Working of the Laser-powdered

A laser pulse with a wavelength of about 2940 nm and a duration of about 250 millionths of a second is released. It makes a vapour inside the driving fluid when it attacks it. The drug is forcedly ejected from a tiny nozzle with a diameter of about 150 millionth of a meter with a very great impact on the skin, sufficient to smoothly penetrate into the skin, without causing any damage to the tissues, and without drug splash back occurring as a result of the bubble that is formed impacting on the membrane, applying pressure to it, and straining it.

The research team is still working on the technology in collaboration with a significant corporation to create better and more sophisticated versions of it.

- **Energy propelled system:**

Commercial spring-powered jet injectors are noisy and occasionally uncomfortable, and they provide little to no control over the pressure that is supplied to the medicine during injection. Energy in a variety of forms can also be used to provide the force necessary to propel the medicine and give it a penetrating effect.

- **Lorentz force**

Researchers at MIT have created an NFIT device that propels a piston forward using Lorentz force to discharge the medication at extremely high pressure and velocity (almost equal to that of sound in air). The device's major part, the Lorentz force actuator, is what makes the whole thing possible (30).

Working of Lorentz force:

The device's design is based on the Lorentz force. Actuator made up of a strong, compact magnet that is encircled by a wire coil that continues to be connected to a piston. It is housed in medicine ampoule. Applying contemporary causes it engages in an interaction with the magnetic field to generate a force , where by the associated piston is propelled forward, and the stream the formulation blasted out of the device is as thin as the an insect's proboscis.

The supply of current can be tightly controlled. allowing the coil's pace to fall under our control. This would eventually be able to regulate the speed at which the medication is discharged. The research group has even shown how the device behaves in a when the medication reaches a high pressure phase and in a low pressure phase with the skin at the optimum strength and for the medicine to be absorbed by the body, it is supplied in a lower stream encompassing tissues The device is now useful because of its ability to flexible NFIT method appropriate for applying drugs to the cornea and suitable for usage by children.

- **Gas propelled/Air forced:**

Gas will be less suited for reusable devices as a power source unless particular adjustments to the arrangement, design, or component may be made to prevent pressure loss, and Despite the fact that the spring is reset for each injection, gas-powered NFITs have wider range because compressed gas has an energy density that is higher than that of a metal spring. Gas powered devices often have a single use or require a regular gas cartridge replacement. Some portable and compact devices use gas as a basic spring to accelerate the piston as it is stored. However, constructing a gas spring that maintains a particular proportion is necessary. It is extremely difficult to get an item to work after it has reached the end of its shelf life**.**

An alternative approach has been developed to address these issues. developed that makes use of liquid carbon dioxide from the storage pressure and temperature. This strategy has produced positive results even a negligible loss of gas from the container causes almost "no" or a pressure drop of "zero." But the strains in such containers are extremely temperature and pressure sensitive between 0° and 40°, doubling. There may have a negative impact on if a wider working temperature range is desired, the device. This pressure regulator can be used to solve
the issue (31).

More investigation has resulted in the development of reusable, complex and, in comparison, more mobile gas-powered NFITs, as in the gadget is powered by a straightforward butane combustion engine (one created by Team Consulting Ltd., Cambridge, (UK).

This system's full efficacy has not yet been determined, and results have not yet been made public.

Cross-Ject and Bio Valve are two significant companies that the creation of NFIT systems has made use of a technology. Chemical process of gas generation, at which the gas is produced, a consistent and dependable rate to power the apparatus. The either a mechanical or electrical response is started, where the gas is produced when a chemical "burns" (32).
The following are the main downsides of this technology:
1. Intricate validation procedures.
2. Noxious stench brought on by reactant combustion.
3. Production of reactants in large quantities.

- **Shock waves:**

Any rapid release of energy results in shock waves. These turbulences can travel through a medium and transport energy. Using this energy at supersonic levels, researchers at the "Indian Institute of Science" (IISc) Bangalore have created a totally noninvasive medicine delivery device.

The following are the main components of the device's prototype:

a. system for starting the "charging."
b. The explosive substance is contained in a polymer tube that has been appropriately coated.
c. Drug loading chamber with drug storing.
d. The cavity holder and metal foils are also included in the system.

A small, "controlled," explosion causes a micro-blast. It has great pressure because it spreads at supersonic speeds. temperature, too. resulting from this "explosion," pressure approach is powerful and effective enough to discharge the medication (a vaccination) to the system created by (IISc) that included a miniature model apparatus. Despite the integrity, the medication is pressed into the skin of the skin is still whole. If the IISc-developed technology is successful, the institute will provide less expensive, noninvasive solutions that will not only stop incandescence needle stick injuries but would also also control infection rates in hospitals.

2. On the basis of type of load:

- **Liquid:**

The earliest NFIT system type was liquid, and it is still in use today. The pharmaceutical industry's top players are collaborating on it .The ability of a liquid jet strong enough to pierce the skin and the underlying fat layer without damaging the skin or the integrity of the drug molecule is crucial to the overall process of a successful injection using a needle-free device. Recent studies have been conducted to fully comprehend the mechanics of liquid NFITs because they are so complicated.

When delivering fluid from NFIT, careful use of fluid dynamics the necessary stages are:
• "Registration": The device's orifice is precisely positioned over the skin's pores.
• Exact pressure: The fluid needs to be pumped at an ideal pressure that is both powerful enough to keep the skin's perforations open and consistent enough to prevent them from resealing.
• Channel drilling: The fluid's initial pulse creates a channel deep enough in the fat layer to allow the dose to diffuse from the hole into the skin.
• Quicker pressure fall: The pressure falls sufficiently and rapidly to prevent fluid from penetrating the muscles beneath the skin (33).

- **Powder**

The ability to manufacture a powder injection without a needle is necessary the particles are strong enough to penetrate the skin, and they are accelerated to a strong enough velocity and number to attain the therapeutic dose levels. This was achieved thanks to the use of helium as a power source and changes made to the drug's formulation processes, such as:

- The transformation of the drug, either in its pure form or combined with excipient, into hard particles measuring 10–50 nm in diameter and having a density similar to that of a crystalline substance.
- The conversion of the medication, either in its pure form or when coupled with excipient, into hard particles with a density like that of crystals, and measuring 10–50 nm in diameter.

Working of powder:
The drug is kept in a "cassette" that is made with the drug in the centre and a polymeric lid on top. When the cassette is activated, a gust of helium gas breaks through the lid and forces the drug forward. Because of specially made convergent-divergent type nozzles, the drug particles reach speeds that are almost as fast as sound, which allows them to penetrate the skin.

Only those applicants with an effective dose of up to 1 mg can receive drugs through this technique. The maximum payload for a 20 mm diameter target region of skin is around 2-3 mg because it is difficult to forecast the proportion of dose that is to be delivered to the epidermis when powder drugs are given by NFIT systems (34).

- **Projectile/Depot:**

Advanced compared to earlier produced NFIT variations, the medicine is processed into a long, thin depot with enough mechanical strength to deliver a driving force to a pointed tip that may be made of the medication itself or an inert material.

A depot typically has the shape of a cylinder with a diameter of around 1 mm and a length of a few millimeters. Although the payload may be limited by this dimension, there are many of new therapeutic proteins, antibodies, and other tiny molecules that can be included. When struck with the sharp-tipped punch, the depot is strong enough to pierce the skin when pressure of between 3 and 8 mega Pascal is applied (MPa). Only a few Newtons of force are needed to prepare a depot that is about 1 mm in diameter. Therefore, the delivery device would transfer energy from an appropriate "spring" onto the target a depot (35).

2. **On the basis of the mechanism of the drug delivery:**

- **Nano –patches:**

The use of an applicator to transfer the medication via the skin is necessary for nanopatch or micro-projection to function. Since nano-patch projections cannot be seen with the human eye, people shouldn't be afraid of them. With regard to vaccines, drug delivery via nano-patches has proven to be particularly effective. The vaccine can be delivered using painless nano-patches to the important immune cells beneath the skin's surface.

- **Sand paper assisted delivery**

The majority of the time, a substance similar to 220 grit "sandpaper" is applied to the skin in order to cause micro-derma abrasion, a phenomenon in which the top layer of skin is destroyed, which facilitates the entire drug delivery process. The use of microdermabrasion for cosmetic purposes is widely approved. For some vaccinations and other types of Microdermabrasion, sandpaper has been useful in enhancing skin permeability, which has been utilised to facilitate the transfer of medications like lidocaine and 5-flurouracil. This method has been used to create vaccines against influenza and traveler's diarrhoea up until now (Clinical trials in progress) (36).

- **Iontophoresis enabled**

Multiple salts and other compounds cannot penetrate the skin because of the lipophilic nature of skin. A modest electric current of approximately 0.5 mA/cm2 is used in iontophoresis to push a number of medication molecules across the skin. In order for this approach to function, two electrode patches are used, one of which serves as a drug reservoir and may be positively or negatively charged depending on the substance being administered. The other patch is applied to another location on the body to complete the circuit.

Both the type of medicine and the quantum of charge (positive and negative) must be compatible with the method for iontophoresis to deliver drugs successfully. The drug's excipients and the state of the skin must also be taken into account. Iontophoresis has proven to be a highly effective method for delivering peptides, therapeutic proteins, vaccines, and oligonucleotides[37]

- **Micro-needles**

Micro-needle patches use thousands of tiny spikes, each measuring around 750 microns in length, as the name suggests. These patches are applied to a person's skin, with the spikes puncturing the epidermis to administer the medication, but not deeply enough to pierce the blood vessels or even the pain receptors to produce discomfort. Micro needles come in a variety of designs, from sophisticated metallic to plastic. While some are merely "coated" with the medication, others are hollow and have the medication or a liquid vaccination contained inside.

Since more dendrite cells which are more sensitive to vaccines are found in the skin, researchers have found that administering drugs mostly vaccines via micro-needle patch is more effective than standard intramuscular injection.

In addition to being extremely effective, micro-needle patches have also demonstrated improved patient compliance. The usage of micro-needle patches does come with some restrictions, though (38).

• Larger doses necessitate larger patches.
• In situations where the needle itself is formed of the drug, the formulation must have the necessary physico-chemical properties to retain a sharp tip for optimal skin penetration.
• The micro-penetration needle's depth may vary. depending on the thickness and toughness of the skin, from person to skin and the application's repeatability.
• The body's movements or those of the body portion that when a patch is applied, the needle could become loose.

On the basis of site of delivery:

- **Intradermal injector**

These methods have been used to deliver DNA-based vaccinations, which are more recent, to the intradermal layer. The medicine is delivered via the system at a very shallow depth, or in the layer of skin (39).

- **Intra muscular injector:**

One of the NFIT systems with the highest level of development used for intramuscular medication administration. This system has the deepest level of drug delivery. The most effective use of NFIT devices for drug delivery has been for immunization (40).

- **Sub cutaneous injector:**

By using this technique, specific therapeutic proteins have been delivered, including human growth hormones. The adipose layer beneath the skin receives the medication (41).

Recent Advances in Needle Free Injections:

1. Serojet:

The system is intended to deliver Serostim, a subcutaneous injection of recombinant human growth hormone. The Vitajet technology is used to create the Serojet gadget. This was authorised for sale by the FDA in March 2001 and is used to treat adult patients with wasting caused by HIV (42).

Figure 4: Serojet

2. Iject:

It is a second gas powdered injection device made by the Bioject Company. The Iject is a pre-filled, single-use, disposable injectable tool designed to deliver injections ranging from 0.5 to 1.00 ml intramuscularly or subcutaneously. The device is initiated by twisting the trigger sleeve 180 degrees. The injection is given with the nozzle pressed up against the injection site by advancing the trigger sleeve (43).

Figure 5: Inject

3. Injex:

Local anaesthetic can be administered using the Injex system. It is made up of an injectable ampoule with a 0.18 mm opening. The medication is shot through this aperture under dosed pressure into the submucosa. The ampoule must be positioned 90 degrees above the tooth to be anaesthetized on the associated gingiva. About 0.3mL32 of local anaesthetic can be used for administration (44).

Figure 6: Injex

4. Bioject®Zetajet:

It is made up of a disposable auto-disabling syringe and a handheld injector. It is indicated for both professional usage and home use by patients who self-inject. It is meant to deliver vaccines and injectable drugs either subcutaneously or intramuscularly. A distinctive "auto disable" feature on the syringe assembly prevents the syringe from being reused (45).

Figure 7: Biojector

5. Vitajet:

In 1996, the FDA gave its marketing approval. It is made of dispensable nozzles for subcutaneous insulin delivery that must be changed once a week (46).

Figure 8: Vitajet

6. Cool click:

It was created by Bioject to administer Saizen's recombinant HGH. Natural growth hormone is lacking or produced in insufficient quantities in some children. To sustain normal growth in these circumstances, Saizen or growth hormone replacement must be injected (47).

Figure 9: Cool click

7. Madajet:

The usual injector in dentistry. To release local anesthesia, pneumatic pressure is used. Below the epithelium, the fine stream of drug formulation penetrates the skin by 4 to 5.5 mm. At the base of injection, this stream creates a wheel with a diameter of around 5 to 6 mm. The apparatus administers 0.1 cc of fluid each intradermal injection (48).

Figure 10: Madajet

8. Mhi-500:

Insulin is administered subcutaneously with this device. In 1996, the FDA authorised the marketing of the system across Europe. Through the nozzle, the gadget emits a tiny jet of insulin that penetrates the subcutaneous layer's skin tissues (49).

9. Recojet:

Shreya Life Sciences' recombinant human insulin is intended to be delivered by the device (50).

10. Intraject technology:

The pre-filled, disposable device resembles a fountain pen. The apparatus works well with liquid protein formulation. In less than 60 ms, the medication is delivered by pushing an actuator with compressed nitrogen (51).

Manufacturing of needle free injection technology:

There are other methods for producing NFIT devices however the discussion that follows provides information on how an air-forced system, as shown in Figure 11, is made.

Raw materials:

The gadget must be composed of pharmacologically inert materials because it will come into direct touch with the skin. The outer compartment or the body of the gadget should be made of polycarbonates, particularly thermoplastics, which are generated synthetically, are simpler to mould, and are lightweight. Colorants are usually, but not always, added. Helium or CO2 are used by gas-powered systems as sources of propulsion; more recent designs use butane. The device's body must be constructed from a material that does not react with gas or other adjuvants, including colourants

To produce the finished product, the raw materials are used in a step-by-step process. Off-site manufacturing produces the individual components, which are then put together by the manufacturer in a sterile environment.

Making a pieces:
The gadgets are made using an incredibly adaptable process known as injection moulding, which is employed in the plastic manufacturing industry forming procedure. In this procedure, the relevant raw materials are mechanically or manually fed into the hopper in the form of pellets.

A spinning screw in the hopper directs the pellets into the machine's cylindrical body. Due to frictional forces created by the pellets gliding over one another while they are being pushed to the nozzle by the rotating screw, the pellets melt. Additionally, the tube may be heated externally to enhance temperature, which may help with melting the pellets and increase flow ability.

With the aid of a screw, the melt is injected into the mould through the nozzle. When the plastic is put into the mould, it is maintained there under increasing pressure for a while before being given time to cool and harden. To release the developed "design," the mould components are opened or separated. Manual inspection is performed on the created design or manufactured device to check for flaws or structural irregularities.

Assembling and labeling:
After being formed, the design is moved to an assembly line where advanced, extremely exact machines mark the design or the pieces. During this step, employees are used to insert numerous distinct compartments to build a complete device. Their markings may be for dose levels etc. At this point, any necessary attachments, such as buttons, etc., are fixed.

Packaging:
The final step is packaging the item when it has been fully constructed and all attachments have been secured. The equipment is placed into cardboard or plastic boxes after being first wrapped with sterile films. These crates contain all the necessary instruction manuals or insects. Then the pallets with the boxes are loaded for shipping.

Quality control:
Line inspectors continuously monitor the whole manufacturing process for any aesthetic flaws or structural irregularities. Along with being measured for thickness and dimensions, the equipment is also examined for accuracy and precession. Inspectors also check the calibration and labelling. These devices may have a number of safety concerns, hence the Food and Drug Administrations have tight regulations regarding their production (FDA). The FDA inspects the production facilities on a regular basis (52).

Applications:
The following medications are frequently used in conjunction with this technique.
1. The best option for needle-free delivery is thought to be insulin, which needs to be delivered multiple times throughout the day.
2. The local anaesthetic lidocaine hydrochloride can be administered without the need of a needle.
3. Several medications can be injected without using a needle, including heparin (an anticoagulant), erythropoietin, lidocaine hydrochloride (a local anaesthetic), and numerous vaccinations.
For the most part, this technology has been successful in delivering a number of newer pharmaceuticals in a form that is acceptable to patients.

CONCLUSION:
Disease transmission by the reuse of needles is a significant problem in the underdeveloped countries. There seems to be a huge market for needle-free technologies in the pharmaceutical sector. Needle Free Injectors are more user-friendly, effective, dependable, significantly safer, and have no disposal issues. Faster injection times than with traditional needles are another advantage.

The most effective way for administering immunizations is needle-free systems because of patient acceptance, ongoing improvements, and falling costs. Not only can it help product sales, but it also can increase adherence to dose instructions and produce better outcomes.

Vaccines, biotechnology treatments that deliver proteins and peptides, genes, and insulin are among of the applications that are anticipated to be crucial to the development of needle-free technologies.

The workforce needs to be instructed in and made aware of this technology. The expense of start-up and training may also influence some producers' interest in this technology. The need for painless drug delivery and the prevention of needle stick injuries is growing, and this bodes well for the future of needle-free injection systems.

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