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Needle Free Injection Technologies: A Review

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ABSTRACT

Despite the fact that the majority of medications are taken by oral, inhalation, transdermal, and parenteral routes, the demand for innovative drug delivery technology is always rising. Needle free injection technology (NFIT) is a very broad concept that comprehends a variety of drug delivery methods that propel pharmaceuticals through the skin utilizing any of the forces as Lorentz, shock waves, pressure by gas, or electrophoresis, effectively eliminating the need for hypodermic needles. This technology is not only claimed to be advantageous for the pharmaceutical industry, but the developing world also finds it to be very helpful in mass vaccination campaigns, obviating the risk of needle stick injuries and preventing other complications, such as those brought on by the repeated use of a single needle. As opposed to conventional needles, this produces an ultrafine stream of high-pressure fluid that can enter the skin without the need for a needle, resulting in speedier drug delivery. Patients and healthcare workers benefit from its inexpensive price. Larger investments have been placed in the development of this technology, and a number of devices are already on the market after receiving FDA permission.

Keywords: - Needle free injection, Delivery, Painless, Design.

1. INTRODUCTION

Many scientists are currently working on technology that promises to improve the effectiveness and reduce the discomfort of administering medication. For protection against cholera, typhoid, tetanus, influenza, and other diseases, people receive injections. A needle's vaccination or medicine delivers systemic immunity when it is inserted through the skin. This is because the vaccination causes the body to produce antibodies that travel throughout the body when injected into the bloodstream. The hypodermic needles used for these injections, however, have a number of drawbacks. [1] Drugs are frequently administered intravenously to treat and prevent a variety of illnesses. However, because it damages tissue, it is an intrusive method of drug administration. It’s possible for diseases to propagate through injections, especially if needles are misused or repeatedly used. In the past several years, needle free injection technologies (NFIT) have become more popular and offer a number of advantages as a means of overcoming challenges associated with injections using needles. These technologies are designed to inject liquid formulations as well as solid particle dosage forms of medications and vaccinations. [2] The phrase "needle-free" is applied to describe a wide variety of drug delivery methods, including those that don't use needles at all but instead employ electrophoresis to push medications through the skin and those that do but still need one or more tiny needles. Alternatives to injections using needles have been developed by many organizations. This technique includes a variety of designs, such as nasal sprays, nose drops, flavored beverages, skin patches, air forced, and edible crops that have been packed with vaccines. In the near future, genetically modified foods might prove to be an effective substitute for administering immunizations. [3]

1.1 Skin structure

Since pharmaceuticals are delivered to the skin using needle-free injection devices, understanding the anatomy of the skin is crucial for efficient drug administration. The epidermis and dermis are the two main layers of human skin. [4]

1.1.1 The Epidermis: Between the body and the outside world, the epidermal layer serves as a physical and chemical barrier. This layer of squamous epithelium is stratified, meaning that it largely consists of keratinocytes and dendritic cells. Melanocytes, Langerhans cells, and Merkel cells are only a few of the other cells found in the epidermis.

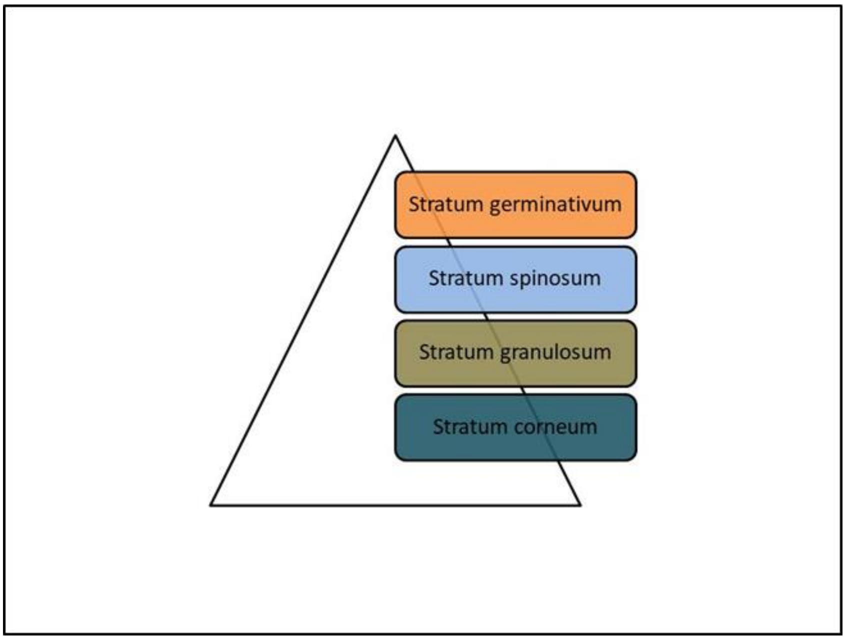

Fig no.1: Layers of epidermis

1.1.2 The dermal-epidermal layer: It supports the epidermis, determines cell polarity and growth direction, controls how basal cells organise their cytoskeleton, transmits developmental signals, and serves as a semi-permeable barrier between layers.

1.1.3 The Dermis: It is a cohesive structure of fibrous, filamentous, and amorphous connective tissue that allows for stimulus-induced entry of mast cells, fibroblasts, vascular networks, and nerves. Its thickness varies between 2000 and 3000 m. Collagen makes up 70% of the dry weight of the skin and is the dermis' primary constituent. Its primary purpose is to safeguard the body against pressure and stress. The dermis-stored mechanoreceptors provide us a sense of touch and heat.

1.1.4 Subcutaneous Tissue: The subcutaneous tissue, also known as the hypodermis, is made up of loose-textured, white, fibrous connective tissue that contains blood and lymphatic vessels and is not truly thought of as a true component of the organized connective tissue. Although the fatty tissue may act as a drug depot, this layer controls the drug's penetration through the skin to enter the circulatory system before reaching the hypodermis. [5]

2 Origin of NFIT

The development of needle-free technology (Jet injectors) in the 1930s led to its widespread usage over the course of 50 years in mass vaccination campaigns against smallpox, polio, and measles. These devices created a high-pressure stream that could penetrate skin and subcutaneous tissue to deliver the vaccine by using mechanical compression to drive fluid through a small aperture. The fluid was typically generated by a compressed gas, usually air, CO2, or nitrogen. The vaccine is delivered to the skin, subcutaneous tissue, and underlying superficial muscle in a fraction of a second when it is injected through the skin using an ultra-fine stream of fluid. The wetness of residual vaccine on the skin surface has been a major issue with needlefree injections, and it may lead the vaccination administrator to believe that the vaccine was not correctly delivered. Without the use of a needle, needle-free injection technology can deliver antibiotics, iron dextran, or vaccines comfortably, correctly, and swiftly. [6, 7, 8, 9]

1.3 Benefits:

- No drug overdose or underdose condition exists.
- Prevents skin puncture risks and its destruction; it also doesn't produce bleeding or bruising issues or much of a skin reaction.
- Delivers drugs more quickly and with better uniformity than invasive drug delivery methods, which improves bioavailability in comparison to those methods.
- Greater drug stability during storage due to delivery in dry powder form, particularly for pharmaceuticals that are water sensitive.
- Improved patient compliance, especially with long-term drug treatment.
- Self-administration is possible; there is no need to go to hospitals or specialists for injections.[10]

1.4 Drawbacks:

- The process is intricate and costly.
- No system may be put into a single size.
- The requirement for staff upkeep and training. [11]

CATEGORIES OF NEEDLE FREE INJECTION TECHNOLOGY

On the basis of working	Spring system
	Laser powered
	Energy propelled system
Type of Load	Liquid
	Power
	Projectile
Site of delivery	Intradermal
	Intramuscular
	Subcutaneous

Fig no. 2: Categories of NFITs

1.1. On the basis of work:

- Spring system: As springs are one of the simplest and most straightforward ways to convey energy, they have been shown to be highly effective in powering needle-free injection technology devices. To prevent the spring from taking a "set" over time and degrading the device's performance, the spring's design must adhere to accepted guidelines and storage conditions must be straightforward.[12]

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. To put it simply, during an injection of a spring-assisted NFIT, the pressure must progressively decrease. [13]

- Laser Powered: An erbium-doped Yttrium garnet laser is used in the technique to deliver a highly fine and precise stream of medication with just the correct amount of force.

There are two chambers in it: An adaptor to contain the medicine to be delivered is built inside the laser. Additionally, it has a water chamber that aids in the movement of the medication. [14]

- Energy propelled system [15,16]:

Lorentz force system

- an NFIT device that drives a piston forward using Lorentz force to eject 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.

- Gas propelled system

  - They could be one-time usage only or require regular gas cartridge replacement. Some systems utilize gas as a basic spring, accelerating the piston as it is stored. These devices are portable and small, however creating a gas spring requires that a certain amount of gas be kept in reserve for use after the gas's shelf life has passed.Because it has a higher energy density than a metal spring and enables the gas to be burned to power the device, this sort of technology has a wider range of applications. spring and enables the gas to be burned to power the device, this sort of technology has a wider range of applications.

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Fig no.3: Types of energy propelled system

1.2. Type of load

- Liquid injections: The fundamental idea behind this injection is that "if a fluid in close proximity to the skin can generate a high enough pressure, then the liquid will punch a hole in to the skin and be absorbed into the body. "supplied to the skin's surface tissues and beneath the skin. The actual design and functionality of the powder injection devices differ, even though the same principle is used as with powder. These systems make use of pistons, nozzles, drug-loaded chambers, gas or springs, and gas. The nozzle typically has an opening size of between 150 and 300 μm. [17]

- Power injection: The fundamental idea entails using the non-reactive gas Helium to generate particles with a compact enough composition and accelerate them to a fast enough speed to penetrate skin at therapeutic dose levels. The particles should be carried by or coated with the vector or medium. [18]

- Projectile injection: The medicine is processed into a long, thin reservoir with sufficient mechanical strength to convey a driving force to a pointed tip, which can be made of either an inert substance or the medication itself. This type of the NFITs is much more advanced than earlier versions. Although the dosage may be limited by this dimension, there are many of new therapeutic proteins, antibodies, and other tiny molecules that can be included. Therefore, the delivery device would use an appropriate "spring" to transmit energy to the depot. [19]

1.3. Site of delivery

- Intradermal injector: These systems play a key role in the administration of relatively more recent DNA-based vaccinations to the intradermal layer and administer the medication at a very shallow depth, i.e., in the space between the skin layers.

- Intramuscular injector: This technique has the most effective drug delivery of all and is mostly utilized for immunization.

- Subcutaneous injector: These systems play a vital role in the distribution of human growth hormones because they make it simple to administer the needed dosage unit into the layer of adipose tissue beneath the skin. [20]

2. DESIGN OF NEEDLE FREE INJECTION

Depending on the medication for which they are used, devices can have a variety of designs.

1.4. Injection device: It is composed of plastic and has a medication chamber. The equipment is kept sterile at all times. [21]

1.5. Nozzle: The medication travels through the nozzle. After injection, the medication penetrates the skin through an opening in it. Usually, the orifice's diameter is 100 m. Drug particles are discharged from the nozzle at a typical speed of 100 m/s and a depth of 2 mm. As a result, the injection is painless; the patient just feels a tap of gas, which feels like a finger snapping against the skin. [22]

1.6. Source of pressure:

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 essential for forcing a medication through the skin and into the bloodstream. Carbon dioxide or nitrogen 20 are the two most frequently used gases in equipment. [23]

3. BASIC REQUIREMENTS OF DRUG FOR NEEDLE FREE INJECTION TECHNOLOGY

1.7. SHELF LIFE: Systems for injection employing needles have a longer shelf life. The device's mechanics must allow it to be activated even after being stored for two to three years under various storage conditions. The following factors must be taken into account during the needle-free injection system's production process and over the full planned shelf life:

- The product must maintain sterility throughout the duration of its shelf life
- Endotoxins and foreign particles must not exceed the predetermined limit
- The leachable profile into the formulation from the device's contact component must not be excessive but rather acceptable
- The purity, composition, and concentration shall not be compromised throughout the duration of the intended shelf-life in any case
- The entire device must be made of a material that is stable and provides good mechanical strength. [24]

1.8. VISCOSITY: The amount of force needed to deliver the medicine increases as the viscosity of the formulation rises. Different viscosities are used in the formulation of needle-free systems, which facilitates simple drug delivery for various formulations.[3][20] 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 non viscous one. Additionally, the additional effort needed increases along with the viscosity. As they don't use any hollow needles, needle less devices are proven effective in delivering a wide variety of formulations with variable viscosities and don't have to deal with these occurrences. [25]

2. MANUFACTURING PROCESS

1.9. Raw material: Fillers are added to polymers to make them simpler to shape, increasing the rigidity, durability, and weight of plastics. To change the appearance of the plastic, colourants are also added. The colourants and fillers are often already present in the polymers when they are given in pellet form prior to production. Some medications perform better with needle-free injection methods than others, and air-forced devices often use carbon dioxide or helium gas to propel the medication into the body. A local anaesthetic called lidocaine hydrochloride can be administered without using a needle. Fentanyl, heparin, and a number of vaccinations are other medications that work well with needle-free systems. [26]

1.10. Manufacturing: Each needle-free injection system can be produced using a variety of techniques. The next method focuses on creating an airforced system. These systems are created using a step-by-step process that entails moulding the components, putting them together, and then decorating and labelling the finished item. The needle free injection system maker normally produces the various parts off-site and assembles them. To stop the transmission of illness, the entire production process is carried out in sterile conditions.

1.11. Assembling and Labelling: Various things happen during this production process.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. [27]

1.12. Making pieces: Manufacturing the component plastic parts from plastic pellets is necessary as the initial step. The technique used for this is injection moulding. On an injection moulding process, plastic pellets are loaded into a sizable holding bin. To make them flowable, they are heated.The material is subsequently forced through a screw that is controlled by hydraulics. 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, held there for a predetermined period of time, and then given time to cool. The plastic inside hardens as it cools.

1.13. Packaging: The injection devices are packaged after the assembling stage.They are placed in cardboard or plastic boxes after being first wrapped in sterile films. To minimise mobility and prevent damage, each component is packed. In addition to safety information, consumer products often come with an instruction manual. These cartons are then loaded onto pallets and transported to distributors by truck.

1.14. Quality control: Line inspectors continuously monitor the whole manufacturing process for any apparent flaws or structural irregularities. Along with being measured for thickness and dimensions, the equipment is also examined for accuracy and precision. 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. [28]

3. MECHANISM

A tiny opening that is pressed up against the skin allows the medicine to be injected without using a needle. The concept for needle-free injection makes use of the force where the medicine is propelled through a small hole at a high speed using compressed gas, such as air, carbon dioxide (CO2), or nitrogen (N2) (Figure 3). This makes it possible for a high-pressure, ultra-fine stream of fluid to penetrate the skin without the use of a needle. When a drug is administered through the skin, an incredibly tiny fluid stream pierces the skin and quickly delivers the medication to the skin, subcutaneous tissue, and intramuscular tissue. Less than 0.5 seconds are needed for the injection event. [29]

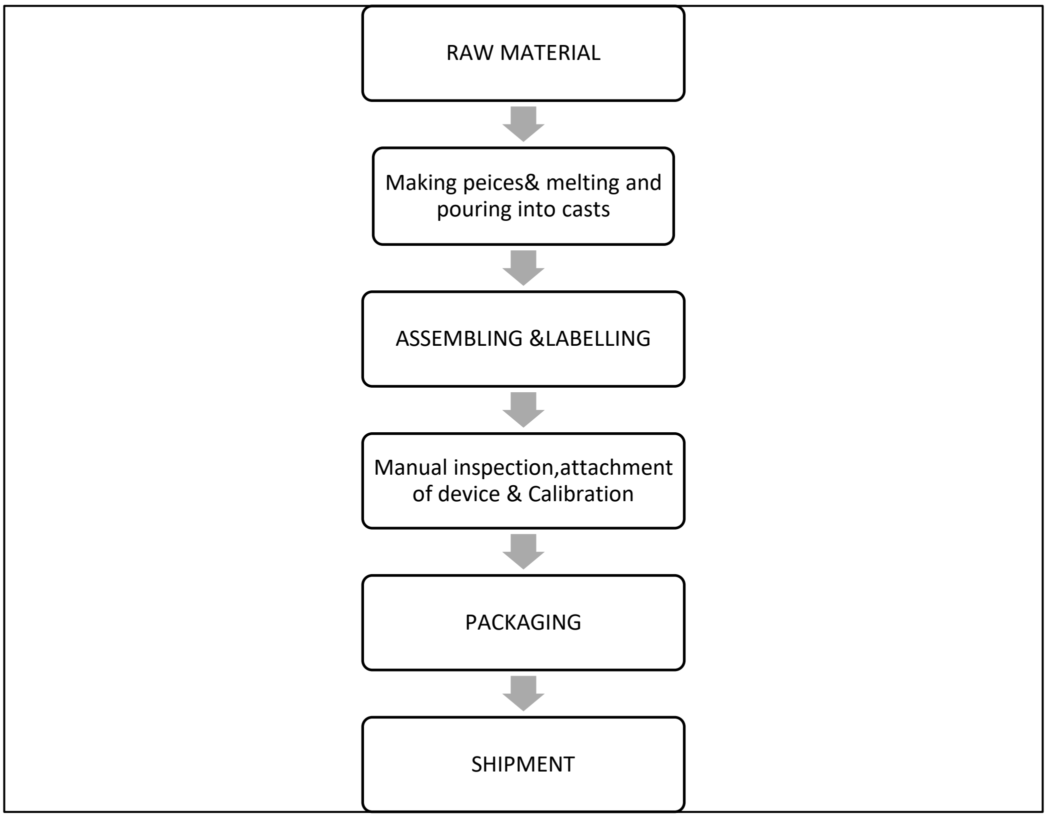

Fig no 4: Process of making an injection

6.1 Stages of delivery of the drug through NFIT

There are three stages to it:

i. Peak pressure phase: during this phase, the skin is penetrated using the best pressure possible in less than 0.025 seconds.

ii. Dispersion phase: Up to 0.2 seconds are spent in the delivery

iii. Phase of drop-off: It lasts for less than 0.05 seconds.

Up to 0.5 seconds are needed to give the medication in its entirety. [30]

4. APPLICATIONS

The following medications are frequently used in conjunction with this technique.

1. Needless administration is thought to be the best option for insulin, which needs to be administered numerous times during the day.

2. The local anaesthetic lidocaine hydrochloride can be administered without the need of a needle.

3. Needleless injections can be used to provide heparin (an anticoagulant), erythropoietin, lidocaine hydrochloride (a local anesthetic), and several vaccines. [31]

4. INJEX, Needle free injections for infiltration anaesthesia: A needle-free injectable method from INJEX Pharma now provides a solution for earlier local anaesthesia issues. The INJEX System delivers the anaesthetic under controlled pressure to the sub mucosa through an injectable ampoule with a tiny aperture of just 0.18 mm, making it almost painless and placing it exactly where it is needed. [32]

5. Pediatric Patients- Children make particularly challenging dental patients because they are so terrified and don't comprehend why the procedure is necessary. Skilled dentists are able to utilize INJEX to give anaesthesia to all deciduous teeth. Children's exposure to treatment-related stress is further decreased by the shorter start period. Considering that only 0.3 ml of local anaesthetic are used. [33]

6. Adult Patients- Many individuals are terrified of both the discomfort associated with getting dental work done and syringes with needles. The "needle-free syringe" can help to solve this issue.

For the most part, this technology has been successful in delivering a number of newer pharmaceuticals in a form that is acceptable to patients. [34]

5. FUTURE PERSPECTIVE

People desire safer and more effective ways to take their medications. Pharmaceutical firms also require new strategies for differentiating their goods in the face of heightened competition, as well as measures to prolong the patent protection of their exclusive treatments. Parenteral administration of many medications and vaccines is necessary, but there is little room for further advancement in the field of auto injectors and pen injectors. So, there will always be a need for fresh technologies, such needleless injection tools. Although liquid jet injectors are now thought to be expensive, which is one of the reasons the technology is not utilized more frequently, the cost will decrease as utilization rises. They might also be able to provide other advantages for liquid formulation, like enhanced stability or controlled release. Although needle based technologies can also provide these advantages, needle free devices will also have the advantages of being simple to use and lacking a needle. The ability to inject solid dose forms will likely represent the most significant developments in needle free injection technology. The main obstacle, however, will be proving that the major perceived hazards of manufacturing scale up and regulatory approval for a novel drug delivery platform can be overcome through the successful commercialization of the first solid dose injection product. [35]

CONCLUSION

Needle-free technology offers the clear advantage of reducing patient concerns about needle use. Another advantage is very fast injection. Compared to conventional needles, Needle disposal is a problem. The pharmaceutical industry not only benefits from increased product sales, but also has the potential to improve medication adherence and improve outcomes. Disease transmission from reusable needles is a major challenge in developing countries. Organizations like WHO CDC (Centers for Disease Control) and groups like Gates Foundation contributed to the development of needle-free Alternative to drug delivery. More than 300 products are in active development due to the biotechnology revolution. A line of protein-based therapeutics is rapidly entering the market. These protein-based therapeutics, especially monoclonal therapeutics Antibodies (MAbs), expected to account for 30% of pharmaceutical sales by 2007, are otherwise difficult to administer. Still available by injection prescribed as a drug. There seems to be a huge opportunity for needle-free technology to have a major impact on the industry. Dramatic changes can occur. A fantastic opportunity exists for needle-free technology that will significantly alter the market. It is clear that spectacular revolutions can only happen when there are huge. The adoption of needle-free technology by pharma or biotech firms will show the technology's adaptability, acceptance, and worth in key therapeutic areas. [36]

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