

NEEDLE FREE INJECTION SYSTEM: A REVIEW

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ABSTRACT

Needle free injection systems are innovative ways to introduce a variety of medicines in patients without piercing the skin with a traditional needle. These systems work by the mechanism in which liquid medication is forced at an elevated speed through a small orifice that is held against the skin. Due to this an ultrafine stream of high pressure fluid is created, that penetrates the skin devoid of the use of a needle, thus faster administration of drug occurs as compared to conventional needles. Needle free systems are designed to solve the problems created due to conventional needles making them safer, less expensive, and more suitable. It is expected that these systems will augment the rate of vaccination and reduce the amount of antibiotics prescribed. Moreover, they should decrease the occurrence of needle stick accidents that have been seen in some health care workers contracting diseases. Today, they are an increasingly rising technology that promises the administration of medicine efficient with reduction of pain. Companies are not only working on developing technologies that are safer and easier to use, but also on alternatives which can deliver more types of medicines.

Keywords: Needle Free, Injection, Drug delivery, Technology.

INTRODUCTION

The term needle free is used to describe an extensive range of drug delivery technologies, which consists of technologies that do not have a needle but make use of electrophoresis to drive drugs through the skin, technologies that use one or more very small needles, but needles nevertheless (Micro needle drug delivery system). Needle free devices can take the form of power sprays, edible products, inhalers, and skin patches. Devices are available in reusable and disposable forms, for home or physicians office use, and also in versions for multiple patients and institutional uses [1,2]. This technology avoids various disadvantages that are associated with needle use:

- The risk of cross contamination from needle stick injury
- Under or overdosing which results in poor injection technique in patients
- Needle phobia
- Injection site pain
- Poor compliance resulting in long term worsening of conditions
- Increased costs due to patients visiting the hospitals for injections

HISTORY

Needle free drug delivery was first projected in the early 19th century with one of the key patents filed by Lockhart in 1930[3]. The first needle free injection systems which were present in the form of air powered devices were developed during the 1940s and 1950.

STRUCTURE OF HUMAN SKIN

Human skin is generally made of two layers i.e., the epidermis and dermis.

Epidermis

It is the external layer of the skin which is mainly composed of various layers of keratinocytes, melanocytes, Langerhans cells and Merkel cells. It acts as a physical and chemical barrier between the body and external environment. The epidermis is stratified squamous epithelium in nature [4,5,6,7]. It has four layers:

1. Stratum basale
2. Stratum spinosum
3. Stratum granulosum
4. Stratum corneum

Dermis

It is the area of supportive connective tissue between the epidermis and subcutis. The dermis mainly consists of sweat glands, hair roots, nerve cells and fibers, blood and lymph vessels. It is mainly composed of a thin papillary and thicker reticular layer. Its main function is to protect the body from stress and strain. A sense of touch and heat is provided by the mechanoreceptors harbored by the dermis [4,5,6,7].

Hypodermis

It is the layer of loose connective tissue and fat that lies beneath the dermis. Its role is to put together the skin and underlying bone and muscle and supply it with blood vessels and nerves [4,5,6,7].

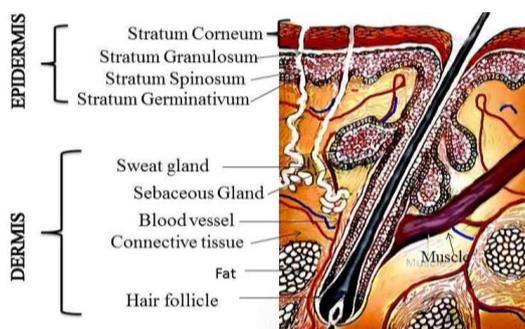


Fig. 1: Structure Of Human Skin[4,5,6,7]

NEEDLE FREE TECHNOLOGY: ORIGIN AND METHODOLOGY

Needle free technology (Jet injectors), were developed in the 1930s and used widely over 50 years in mass vaccination programs in patients suffering from smallpox, polio, and measles. Mechanical compression is used to force (generated by a compressed gas typically air, CO₂ or nitrogen) fluid through a small orifice, these devices created a high pressure stream that could easily penetrate the skin, subcutaneous tissue and underlying shallow muscle in order to deliver the vaccine in a fraction of a second. One major problem to needle free injections has been the wetness related with residual vaccine on the skin surface. Needle free injection technology has been designed to deliver antibiotics, iron dextran or vaccines comfortably, accurately, easily and rapidly without the application of a needle. Needle free injection is precise, reliable, and virtually the same every time. There are 3 stages in needle free delivery: Stage 1, the peak pressure phase, in which optimal pressure is used to penetrate the skin (< 0.025 sec); Stage 2, the delivery or dispersion phase (~ 0.2 sec); and Stage 3, the drop-off phase (< 0.05 sec). As the fluid stream passes through the tissue, a path of least resistance is followed, resulting in a broadly dispersed, and spider web like distribution of the medication [8,9,10,11].

TYPES OF NEEDLE FREE INJECTION SYSTEMS

Needle free technologies are of three types:

1. Powder injections
2. Liquid injections
3. Depot or projectile injection.

1. Powder Injections

For the purpose of delivery via skin, the particles must only pierce the outermost barrier of the skin i.e. the stratum corneum. So, drugs delivered reach the circulatory system at a faster rate as compared to those administered by subcutaneous injection.

The principle of all the devices is the same; i.e. the energy generated by a transient gas jet is used to accelerate a premeasured dose of particulate drug formulation [8,9].

2. Liquid injections

The basic principle of this injection is, if a high enough pressure is generated by a fluid, then the liquid will punch a hole into the skin and will be delivered into the tissues in and under the skin [8,9,10].

3. Depot injections

Depot injections are given in the muscle, where they create a depot of a drug that is released continuously over a specified period of time [8,9,10].

DESIGN

The air forced needle free injection systems are usually made up of three components which include an injection device, a disposable needle free syringe and an air cartridge. The injection device, syringe is fabricated of a durable plastic. The syringe is sterilized prior since it is the only piece of the device that touches the skin. The syringe is fabricated such that, it should be disposed after every use [12,13,14,15,16].

RAW MATERIALS

Since these devices directly come in contact with the body, they must be fabricated from pharmacologically inert materials. The materials must be capable to endure high temperatures since they are heat sterilized. Air forced injection systems are available in different shapes and sizes. The external body of the device is made up of a thermoplastic which has characteristics such as high strength, lightweight. The example of such thermoplastic is polycarbonate. In order to make the polymer significant to mold, fillers are added. Due to the addition of fillers the plastics become more durable, lightweight, and rigid. To modify the overall appearance, colorants are included into the plastic [12,13,14,15,16].

THE MANUFACTURING PROCESS

There are various methods of producing needle free injection system. The manufacturing process involves steps such as molding the pieces, assembling them, decorating and labeling the final product. All of the manufacturing process is done under sterile conditions to avoid the spread of disease [14,15,16].

a. Molding the pieces

It involves production of the component plastic pieces from plastic pellets. This is done by a process called injection molding.

b. Assembling and labeling the pieces

Pieces are inserted into the main housing and buttons are attached. Machines apply markings that show dose levels and force measurements.

c. Packaging

Injection devices are first wrapped in sterile films and then put into cardboard or plastic boxes. These boxes are then stacked on pallets.

QUALITY CONTROL

Quality control checks are performed regularly during the manufacturing process. Line inspectors ensure that the plastic components match with the previously determined specifications. Dimensions such as size and thickness are checked by test methods such as visual inspections and measuring equipment dimensions. Laser micrometers, calipers and microscopes can be used to test the systems. Inspectors also confirm that the labeling and printing on the device is proper and complete and all parts are properly assembled in the device. Production of needle free devices is totally controlled by FDA due to the safety issues. Each manufacturer is expected to follow various production standards and specifications. Announced and unannounced inspections are regularly conducted to ensure that the companies are following good manufacturing practices (GMP). The manufacturers must also maintain a detailed record of production and design operations [8,12,13,14,15,16].

MECHANISM OF WORKING

Needle-free injection technology uses force generated by a compressed gas (typically air, CO₂ or nitrogen) to propel the vaccine at high velocity through a tiny orifice. When administered through the skin, an ultrafine stream of fluid penetrates the skin, delivering the vaccine in a fraction of a second to the skin, subcutaneous tissue, and intramuscular tissue. Injection event requires less than 0.5 seconds [17].

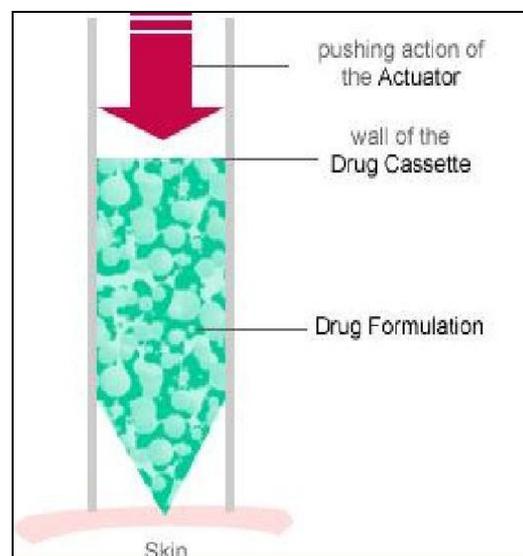


Fig. 2: Mechanism Of Working Of Needle Free Injection System[17]

STAGES OF DELIVERY

There are three stages in the needle free drug delivery:

1. The peak pressure phase-optimal pressure used to penetrate the skin (<0.025 sec)
2. Delivery or dispersion phase (upto 0.2 sec)
3. Drop off phase (<0.05 sec)

The total amount of time required to deliver the vaccine is upto 0.5 seconds [8,18,19,20].

COMPONENTS OF THE NEEDLE FREE INJECTION SYSTEMS

1. Nozzle

The nozzle has two significant functions; it acts as the passage for the drug and as the surface which contacts the skin. The nozzle contains a flat surface and an orifice. The nozzle provides the surface which comes in contact with the skin and the orifice which the drug passes through when injected. The orifice controls the drug stream diameter and speed. A stream diameter of approximately 100 µm and traveling at 100 m/s can achieve the desired injection depth of 2 mm [8,9].

2. Drug reservoir

The drug volume holds the injection fluid inside the device [8,18,19,20].

3. Pressure source

The energy source provides the essential driving energy to the drug for injection. Many of the devices in the market use either mechanical or stored pressure as energy storage elements. The mechanical method stores energy in a spring which is released by pushing a plunger to provide the necessary pressure. The pressure storage method uses compressed gas in a vessel which is released at the time of injection [8,18,19,20].

TYPES OF NEEDLE FREE INJECTION DEVICES

Needle-free injection devices can be divided into 2 types based on the source of power:

1. Spring-Powered:

Compact and lower cost, but suffer from limited range of force and reduced versatility. Spring-powered devices have been primarily used for subcutaneous administration of drugs [8].

2. Compressed Gas-Powered:

Sustained force of generation, greater flexibility, and the ability to deliver larger volumes [8]

DIFFERENT TECHNOLOGIES [21-29]

1. Bioject's needle free injection technology

Bioject has developed an extensive technology platform for delivering variety of medications and vaccines to the subcutaneous and intramuscular depths.

Dispersion Patterns

Bioject's needle free injection technology enhances the dispersion of medication all over the tissue; it follows the pathway of smallest amount of resistance, which results in the uniform distribution of the medication.

[A] Bioject's new Intradermal (ID) Pen spring powered needle free injector Intradermal (ID) Pen Injector

Bioject's ID Pen spring powered needle free injector is proposed to be used for intradermal injections for vaccinations and drug therapy. The system mainly consists of a hand held, user filled device that incorporates single use, and auto disable disposable syringes. The ID Pen is designed to deliver medications in doses such as 5 ml or 10 ml for each injection. The device is totally mechanical and is intended for administration by trained clinicians and properly trained users in home settings.

Iject® and Iject® R

Iject is a small, lightweight, gas powered injection system fabricated for home or professional use. This system has two versions, one is a pre-filled, single use disposable injector, and the other is a reusable injector that consists of prefilled medication cartridges.

Intradermal Syringe

Intradermal injections are shallow as compared to other injection types. They are very complicated to administer with a traditional needle because of the lack of skill and exactness required to deliver them properly.

Jupiter Jet

The Jupiter Jet is an exclusive hand held device that is capable of administering small volumes (0.03 to 0.2 ml) of drugs at SC, IM or ID depths.

Multi-Port Orifices

Bioject is also developing multi-port orifices for enhanced intradermal injections. This novel injector nozzle allows for a greater dispersion of injectable materials, improving the delivery and therapeutic effect of the drug. For many vaccines that require an intradermal injection, this new development could offer noteworthy benefits.

[B] The ZetaJet™

Bioject® ZetaJet™

The Bioject® ZetaJet™, is a Bioject's most recent advance in needle free delivery systems, which consists of components such as the portable injector and an auto disabling disposable syringe. It is used in subcutaneous and intramuscular delivery of vaccines and injectable medications. The unique auto-disable characteristic of the syringe assembly avoids reuse of the syringe. The device has FDA clearance for administering subcutaneous or intramuscular injections of liquid medication, which includes vaccines and other injected medications.

Advantages

Capability to deliver to all three injection depths: Intramuscular, subcutaneous or intradermal. Injection volumes range from 0.05ml to 0.5ml. Leverages Bioject's unique, patented pressure profile. Indicated for both professional and patient self injection. Polycarbonate syringe provides exceptional strength, clarity and heat resistance. Reliable stainless steel inner core enhances durability in rough environments.

2. Biojector 2000

The Biojector 2000 is a tough, professional grade injection system designed especially for healthcare providers. In this technology use of sterile, single use syringes for individual injections is done, which avoids the cross contamination that has been previously reported with fixed nozzle jet injection systems. Biojector is an ultimate injection system for delivering injections to patients suffering with HIV or Hepatitis.

3. Vitajet 3

The Vitajet 3 is a user-friendly, economical needle free injection system for the delivery of insulin that received the FDA marketing clearance in 1996. It has disposable nozzles that can be replaced once a week, the Vitajet 3 is a reusable medical product, with the ease and safety of a sterile disposable.

4. Cool click

Saizen recombinant human growth hormone is delivered by means of this technology which is developed by Bioject.

5. SeroJet

The SeroJet is a needle free injection system intended for the delivery of Serostim recombinant human growth hormone and is mainly used for the treatment of HIV associated wasting in adults.

6. Iject

The Iject is a single use, disposable, pre-filled injection device which can be used in the delivery of subcutaneous or intramuscular injections. No additional parts or modifications are required for function.

7. Biovalve's Mini-Ject technology

It can be used in targeting drugs to intradermal, subcutaneous or intramuscular levels over an extensive range of 0.1 to 1.3ml.

8. Antares' Medi-Jector Vision technology

Human growth hormone, insulin can be delivered by this technology. Due to its plastic, disposable needle free syringe the patient can see and monitor the dose prior to injection.

9. Implaject

Simple, hand held needle free injection device.

10 Crossject

Prefilled, single use disposable NFI. The mechanism of administration involves the use of a chemical reaction which generates propellant during administration.

11 Powderject

Painless delivery of DNA vaccines to the skin in a dry formulation can be achieved by this technology.

12 Zoma-jet 2 Vision

Customized version of Medi-Jector vision, intended for the administration of human growth hormone, Zomacton.

13 Valeo (MJ8)

Intended for use with drugs in cartridge containers, instead of vials. Its clinical trials are completed and it is available for licensing. It is a pen style, spring-powered device

14 SQ-PEN technology

The SQ-PEN was developed by Medical House Products Ltd and has been owned by Diabetes Management International since October 2007. The SQ-PEN uses pressure from a spring loaded piston to create a fine stream of insulin through a small bore nozzle. The pressure and speed of exit of the insulin stream causes it to penetrate the skin, delivering insulin to the subcutaneous layer. SQ-PEN uses a plunger which is activated when there is sufficient depression of the nozzle tip into the skin.

DIFFERENT DESIGNS OF NEEDLE FREE INJECTION SYSTEM:

Include nasal sprays, nose drops, flavored liquids, skin patches (INTERCELLS needle free injection system by FAST COMPANY), nasal shots, inhalers, air forced and edible vaccine-packed vegetables [8].

APPLICATIONS OF NEEDLE FREE INJECTION TECHNOLOGY [30,31,32,33]

1. Mass immunizations such as measles, smallpox.
2. Intraject (Weston medical) technology is used to deliver drugs which consist of proteins, peptides, monoclonal antibodies, small molecules and vaccines.
3. Powderject (Powderject pharmaceuticals) technology is used to deliver insulin to hairless guinea pigs, delivery of large macromolecules across the skin, for intradermal DNA immunization against influenza virus in mice.
4. Jet injectors technology delivers proteins such as β -interferon as well as small organic conventional therapeutic agents such as lidocaine (lignocaine) for local anaesthesia.
5. The Disposable Syringe Jet Injector (DSJI) Project is supporting clinical research on the delivery of vaccines with jet injectors. Current research work includes following applications

a. Inactivated polio vaccine

Inactivated polio vaccine has a long history of safety and effectiveness; additionally, it will be significant following the eradication of polio worldwide once oral polio vaccine is no longer used. Intradermal delivery at reduced doses could widen vaccine supplies and reduce costs to programs, improving access to this important vaccine in the developing countries. Jet injectors, which offer a simple approach to intradermal injection, could facilitate uptake of this vaccination strategy.

b. Influenza vaccine

Seasonal influenza vaccine is often omitted from national immunization programs. This study examined the safety and effectiveness of flu vaccine when given to toddlers in the Dominican Republic. This study tested whether a fractional dose given intradermally by jet injector works as well as a full dose given with a standard delivery method.

c. Intradermal delivery landscape

In conjunction with Project Optimize, the DSJI project supported a literature review to evaluate the landscape of intradermal vaccine research. The resulting report provided an overview of clinical research on intradermal vaccination and intradermal delivery devices and reviews the vaccines which are most suitable for future research on intradermal delivery for application in developing country immunization programs.

d. Measles-mumps-rubella vaccine

PATH is conducting a study to inspect the safety and effectiveness of this childhood vaccine when given by jet injector.

e. Yellow fever vaccine

This vaccine is given in endemic areas of South America and Africa, as well as to travelers from other countries; there are cyclic shortages of this vaccine. Reduced dose intradermal delivery by jet injector could alleviate shortages and increase access to yellow fever vaccine.

f. DTP-Hib-hep B vaccine

This is a type of combination vaccine, which protects against diphtheria, tetanus, pertussis, haemophilus influenzae type b (Hib) and hepatitis B.

PATH's planned research will contrast delivery of this vaccine to delivery with a needle and syringe.

g. BCG vaccine

This vaccine is used in children for protection against tuberculosis. It is given intradermally, but there are challenges with the standard intradermal injection method. DSJIs may prove to be a safer and more reliable means of administering this vaccine.

h. Rabies vaccine

Intradermal delivery of decreased doses of rabies vaccine has been accepted by the WHO. Use of intradermal delivery devices could augment the ease of use of this life saving vaccine.

6. Insulin Therapy

a. The mhi-500 needle-free device is used:

It uses a spring, which is housed within the body of the device. A simple twisting motion winds up the spring and a button is pressed to discharge the energy generated by the recoil of the spring.

b. SQ- Pen injector is also used.

- c. Medi-Jector vision The Medi-Jector vision can deliver up to 50 units of U-100 insulin.

Dosage needle free insulin injection system:

- adjustments can be made in single unit increments.

7. Animal Pharmaceuticals:

MS Pulse250 system is used.

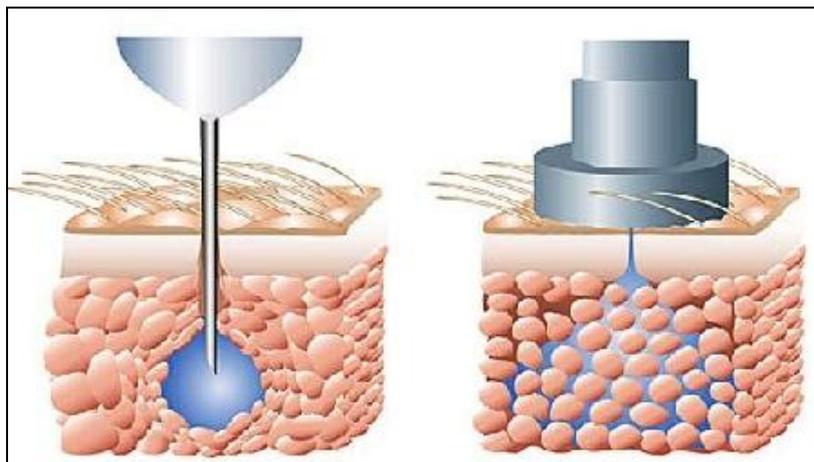


Fig. 3: MS Pulse 250 System [33]

ADVANTAGES OF NEEDLE FREE INJECTION TECHNOLOGY [34]

1. Eliminates needle phobia
2. Increases patient compliance and vaccination rate
3. Elimination of broken needles
4. Consistent vaccine delivery
5. Reduced vaccine volume
6. Higher dispersion pattern
7. Elimination of worker needle sticks
8. Elimination of needle disposal
9. Lower pain and stress
10. Targeted immune response
11. Fewer injection site lesions

DISADVANTAGES OF NEEDLE FREE INJECTION TECHNOLOGY[34]

1. Higher start-up costs
2. Trained personnel
3. Lack of worker confidence
4. Wetness associated with residual vaccine on the skin surface

THE FUTURE

Many of the needle free technologies are in the growth stage. Companies are working on producing devices that are harmless, easier to use & can deliver more types of medicines. Inhalers, nasal sprays, forced air injectors and patches are being developed. In the near future, genetically enhanced foods may prove as an alternative for the delivery of vaccines and other drugs. These include foods like bananas and tomatoes. Actually, bananas are looked as carriers for vaccines to defend against the Norwalk virus and tomatoes for protection against hepatitis B. Besides these novel delivery systems, scientists are also investigating methods for producing long lasting drugs that will minimize the number of needle injections [35,36].

CONCLUSION

Needle free technology offers the very apparent benefit of minimizing patients fear regarding the use of needle. Other benefits comprise very fast injection as compared to traditional needles and needle disposal issues are rarely seen. Not only it can assist the pharmaceutical industry in rising product sales, but also it has the extra potential to increase conformity with dosage regimens and enhanced outcomes. In the developing world, there are foremost challenges of disease transmission due to reuse of needles which can be overcome by the use of Needle free injection technology. Various

supporting organizations and groups are involved in the advancement of needle free alternatives for drug delivery. The biotech revolution is bringing a series of protein based therapeutics into the market place at rapid speed, more than 300 products in active development. This protein based therapeutics particularly monoclonal antibodies (MAbs), which are likely to represent 30 percent of pharmaceutical sales by 2007 and which are complicated to deliver non-invasively, will prolong to be formulated in the form injectables. There is a remarkable opening for needle free technology that will have a key impact in the industry. It is obvious that spectacular revolution may occur only when large pharmaceutical or biotechnology companies will adopt needle free technology and demonstrates its flexibility, acceptance and value in major therapeutic areas [37,38,39,40].

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