Asian Journal of Medical and Pharmaceutical Sciences

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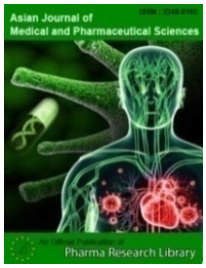

R E V I E W A R T I C L E

Review on Needle Free Injection Systems

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A B S T R A C T

Needle free injection technology was developed to reduce the number of needle stick accidents and associated problems. Advantages over needle injections, their components and types such as powder injection, liquid injection, depot or projectile injection. This describes needle free injection technology involving the generation of force by using compressed gas upon actuation in order to deliver a drug at very high speed through a nozzle. It also describes injection methods that use a spring load jet injector, battery powdered jet injector, and gas powdered jet injector. An overview of marketed products, recent trends and other needleless drug delivery systems is given. Needle free injection technology is growing and has the potential to make the administration of medicine more efficient, safe and convenient.

Keywords: Needle free injection technology, Novel, Powder injection, Liquid injection, Depot, Projectile injection, jet injector.

A R T I C L E I N F O

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ARTICLE QR-CODE

A R T I C L E H I S T O R Y: Received 19Aug 2019, **Accepted** 29 September 2019, **Available Online**19 December 2019

Citation: *CH. Kavya.* Review on Needle Free Injection Systems.*A. J. Med. Pharm, Sci.*, 2019, 7(2): 66-71.

C O N T E N T S

1. Introduction 66
2. Mechanisms 68
3. Advances in needle free injection technology. 69
4. The Future 70
5. References. 71

1. Introduction

Injections are a popular mode for delivering drugs in order to prevent and treat various diseases. But it is an invasive method of drug administration as it causes tissue damage. Injections can be a source of disease transmission, particularly when needles are re-used and used incorrectly. To overcome obstacles related to needle based injections, needle free injection technologies (NFIT) have gained popularity during the past few years and offer many benefits. These technologies are been meant for injecting liquid formulations, as well as injecting drugs and vaccines

in a solid particle dosage form. Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. 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]. There are both advantages and disadvantages of needle-free injection technologies.

Needle-free injection devices (NFID) have been available for humans since the 1930s. According to the International Organization for Standardization (ISO) needle-free injection is defined as the injection of medicinal products through the skin by pressure without penetrating the skin with a needle [ISO/TC 84/WG 4 2004]. The concept "jet injection" is often used as a synonym for needle-free application1 . Their implementation in farm production systems has been slow because of the low expense and ease of use of needle-syringe injection.

Immunology research indicates that targeting dendritic cells in the skin and the subcutaneous tissues results in improved immune response with minimal antigen doses.Due to the factors there has been a renewed interest in needle free injection devices in farm animal production systems.

Needle-syringe devices have been the predominant method for vaccine and drug delivery for dairy cattle. Although needle-syringe devices are inexpensive and easily adaptable to different settings, needle-free technology offers significant advantages compared to conventional vaccine delivery methods including enhanced safety, enhanced immunogenicity, and fewer injection site lesions.

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

Spring-powered or **compressed gaspowered:**

Spring-powered devices are compact and having lower cost, but available in limited range of force and reduced versatility. This device have been primarily used for subcutaneous administration of drugs. Gas-powered devices (jet injectors) have sustained force generation, greater flexibility, and the ability to deliver larger volumes. The main disadvantage is its reliance on an exhaustible energy source. Jet injectors have been used for mass vaccinations and can deliver the target molecule at a variety of tissue depths ranging from the dermis to the muscle depending on the force generated by the jet injector. The vast majority of vaccine trials in animals have used gas-powered jet injectors.

Needle-free injection techniques can be used to administer vaccines and medications in the pork industry. Needle-free injection offers a fast, effective route of administration.Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle.

The first hypodermic syringes were first developed by French surgeon, Charles Gabriel pravaz, in 1853, although there is a minor development in syringes since then, the technology has been remained unchanged for last 150 years. Needle-free systems was 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. These devices were used extensively to inoculate against infectious diseases and were later applied more generally in large scale vaccination program. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful.

Advantages[3]

Advantages of needle-free injection

1. Prevent skin puncture hazards and its destruction; also does not cause problem of bleeding or bruising and minimal skin response.
2. Imparts fast drug delivery and better reproducibility as compared to invasive drug delivery systems and hence enhance bioavailability when compared with invasive drug delivery systems. 3. Better drug stability during storage as it is delivered in dry powder form especially for water sensitive drugs.
4. Avoids problems of reconstitution and any effect of shearing.
5. Elimination of needle phobia.
6. Self-administration is feasible with needle free injections.
7. Improves immune response to vaccines. Immunization of influenza, tetanus, typhoid, diphtheria, pertussis, and hepatitis A vaccines can be delivered by needle free injections.
8. Bio-equivalence has been demonstrated enabling the development of generic drug proteins.
9. A good dose response with increased drug doses.

Disadvantages of needle-free injection[3]

1. Method is complex and expensive.
2. All systems are not fitted into one size.
3. Need for personnel training and maintenance.
4. It is not applicable for Intravenous route.

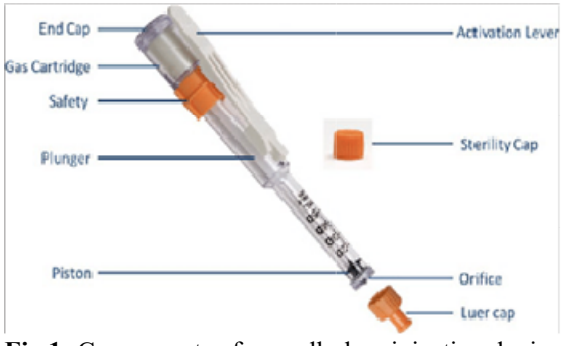

Fig 1: Components of a needle-less injection device

Needle-free injection devises consists of three main components:

Component 1 - Injection device:

It has a drug chamber and is designed such that self-administration is possible. The device made up of plastic. Sterility is maintained throughout the device. It has a sterilized needle-free syringe which is made of plastic.

Component 2 - Nozzle:

The nozzle serves as passage for the drug and serves as the skin contacting surface. The nozzle has an orifice through

which the drug enters skin when injected. The diameter of orifice typically is 100 µm. The nozzle fires drug particles at a typical speed of 100 m/s with a depth of 2 mm. The most common orifice size is 0.127mm, comparable to a 25-guage needle. Therefore this injection is painless; the patient feels tap of gas on the skin which is like flicking your finger against your skin.

Component 3 - Pressure source3:

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. It can also be a pressure storage method that utilizes compressed gas in gas cartridge as shown in Figure 1. The most popular gases used in devices are carbon dioxide or nitrogen. Pressurized metal air cartridges are often provided for access in portable units. The precision of drug delivery and stress imposed on the product is influence by device design. The device must assure the generation of sufficient high pressure to cause skin puncture as well as not harming the drug molecule. Fragile drug molecules are susceptible to damage due to high pressure like monoclonal antibodies. Hence, devices may vary in design depending upon the drug for which they are used.

2. Mechanisms

The mechanism generates force by using compressed gas (such as carbon dioxide or nitrogen) to propel the drug through an orifice at a very high speed. While administration of drug occurs through the device, an ultra-fine stream of fluid penetrates through the skin layers which delivers the drug very quickly into the systemic circulation. The total time required to deliver an injection is less than 1/3 of a second and occurs in three stages:

- Peak pressure phase - optimal pressure requires penetrating the skin which last about < 0.025 sec.
- Dispersion phase - which last about 0.2 sec.
- The drop-off phase - which last about < 0.05 sec.

Types of needle free injection systems:

Needle-free injection drug delivery systems are classified as follows[5]:

1. Powder injections
2. Liquid injections
3. Depot or Projectile Injection.

System Type 1 - Powder injections

Design of powder injection systems

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 injection has a diaphragm (a few microns thick) on either side of the chamber to cover the drug chamber[5].

Mechanism of powder injection:

- Particles exist from the nozzle along with a gas stream.
- Particles impinge the skin surface leading to formation of a hole into the skin with the progression of the injection.
- Drug particles get deposited in a spherical pattern at the end of the hole and penetrate across the stratum corneum.
- After their penetration into the skin, drug particles get distributed completely into the stratum corneum and the viable epidermis.

Powder injection is accomplished by a light gas gun. It provides the required particle velocity by use of an accelerating piston which accelerates and carries particles with it. Particles leave piston surface by means of a deacceleration mechanism which slows down the piston. This leads to ejection of particles that act on the target tissue area[6].

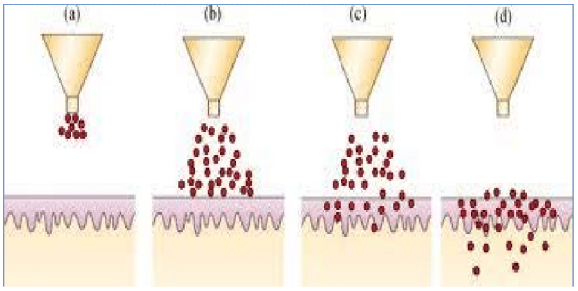

Fig 2: Mechanism of Powdered Injection

Ideal characteristics of powder particles[7]

- In the case of powder injections the drug particle size distribution, quality, its physical and chemical stability are extremely important.
- Powder in an injection may be a whole drug or a formulation containing drug with excipients for dilution purposes or to stabilize the product. Therefore, drug and other excipients must be compatible with each other.
- Particle size plays an important role in penetration into the stratum corneum; hence it should remain uniform throughout usage and storage.
- The particles must be robust enough to survive the highly energetic gas jet within the device as well as ballistic impact with the skin. As the particles strike the skin at a high velocity, they must be strong. The particles have been clocked as fast as 900 meters per second, with 400 to 600 meters per second being the more typical range.
- In order to exert required effects in the body after being absorbed into systemic circulation, the drug particles should have proper diffusion within the skin.
- For skin penetration at a high velocity, the powders must have particle densities of about 1g/cc and mean diameter greater than 20 µm.
- In these injection systems, the powders are processed by compression, milling, sieving, and more scalable methods like spray drying, freeze drying, fluid bed drying, spray coating of seed particles, solution filling and drying pre formed hydrogel beads and emulsion techniques to form erodible micro particles.

Advantages of Powder injections[6,8]

- ✓ A small volume of material, shot through the skin as drug, is in powder form instead of liquid form, hence injection is painless.
- ✓ The therapeutic agent will be more stable and there is no need of cold storage.

- ✓ 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.
- ✓ Protein drugs are very potent, and suitable for powder needle free injection systems.

System Type 2 - Liquid injections:

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 in to the skin and be delivered in to the tissues in and under the skin." Although the same principle is applied as in powder, there is a difference in the actual design and operation of the powder injection devices. These systems use gas or spring, pistons, drug loaded compartments and nozzles. Typically, the nozzle has an orifice size of about 150 to 300 μm[8].

Mechanism of liquid injections:

Impact of a piston on a liquid reservoir in the nozzle increases the pressure, which shoots the jet out of the nozzle at high velocity (velocity > 100m/s) . The effect of the jet 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 jet increases the depth of the hole in the skin. If the volumetric rate of hole formation is less than the volumetric rate of jet impinging the skin, then some of the liquid splashes back towards the injector.The accumulation of liquid in the hole occurs because of a deeper hole in skin which slows down the incoming jet. Hence, further development of a hole is stopped. 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[6].

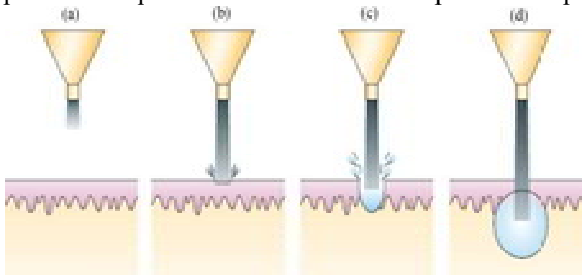

Fig 3: Mechanism of a liquid injection

System Type 3 - Depot or projectile injections

These systems are designed for administration of a drug into muscles. They create a store of drug into muscles that is released continuously over a desired time period[8].

Types of injection methodsinclude[9]:

- Spring load jet injector
- Battery powdered jet injector
- Gas powdered jet injector

Spring load jet injector:

This method works on a spring mechanism which is drawn back. The spring is released by hitting trigger leading to generation of jet stream of drug for subcutaneous, intramuscular or transdermal delivery of a drug. The activated spring load must be redrawn manually for the next administration[9]. Examples: Dermojet® [10], Medi-jector® [10]

Battery powdered jet injector:

This method has a small rechargeable battery pack to retract the dosing device. The dosing device has an electric piston which is automatically redrawn after dosing. This is good for continuous use. This type of injector is similar to a battery powered hand drill. Used for subcutaneous, intramuscular or transdermal delivery of drug depending on the recommended method[9]. Examples: Intra Dermal Application of Liquids (IDAL) ® - Intervet, Boxmeer. [10]

Gas powdered jet injector:

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. [9] Examples: Biojector® [10], Pulse® [10] Needle-Free - Felton [10], Lenexa, Ks. Agro-Jet® /Med-Jet® - Mit[10], Montreal[10], Quebec [10],Canada [10].

3. Advances in needle free injection technology

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. More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. This system proved to be safe and successful in the case of higher risk conditions like delivering drug to HIV or hepatitis infected patients[13,14].

Fig 4: Biojector

VITAJET:

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

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.

Fig 5: Serojet needle free injection device

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[16].

IJECT:
The device is meant for prefilled single use, disposable use for subcutaneous or intramuscular administration. It is a product of the Bioject Company as a second generation gas powdered injection system. The device is initiated by rotating the trigger sleeve 180 degrees. By advancing the trigger sleeve, the injection is administered, where the nozzle is placed against the injection site. [16]

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[16].

RECOJET:
The device is designed to deliver recombinant human insulin which is developed by Shreya Life Sciences[16].

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[16].

Biovalve's Mini-Ject Technology:
The device is simple to use, pre-filled, disposable. Device is suitable for delivering large proteins, fragile antibodies and vaccines. Used for intradermal, subcutaneous and intramuscular administration.

Antares Medi-Jector Vision Technology:
The device is developed for delivering insulin. It is reusable, spring-powdered and able to deliver variable doses[16].

Needle Free, Auto and Pen Injectors[16]:
These are spring loaded syringes meant for administration of a single dose. Auto injectors are popular in the market because of their acceptance by patients and safety profiles. These injectors are promising as new design involves second pre-filled single use device containing a standard prefilled single use device as well as standard pre-filled syringe that automates needle insertion, drug delivery and automatically covers the needle after use. This kind of design shields the needle tip. Such a design provides safety against accidental firing.

Examples include:

- Anapens, Epipens, Twinjects for anaphylaxis.
- Rebiject, RebijectII for multiple sclerosis.
- Sureclick autoinjector which has Enrel or Aranesp drug for treatment of rheumatoid arithritis.

Pen injectors consist of pen cartridges. Using an insulin syringe and needle, a patient's prescribed dose can be withdrawn from pen cartridges. These pen cartridges can be used as multiple dose vials[16].

MADAJET:
The injector commonly used in dentistry. It works by using pneumatic pressure to discharge local anesthetic. The fine stream of drug formulation penetrates the skin about 4 to 5.5 mm below the epithelium. This stream makes a wheel of about 5 to 6 mm in diameter at the base of injection. The device injects a volume of 0.1 cc per injection intradermally[17,18] .

Fig 6: Madajet XL needle free injector

BIOJECT-ZETAJECT:
This system has a portable injector and auto disabling disposable syringe. It is suitable for subcutaneous and intramuscular use. The system injects a volume range from 0.05 mL to 0.5 mL[16].

Fig 7: Bioject ® - Zetajet

Injex Needle Free Injections for Infiltration Anesthesia:
This device has an injection ampoule having 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[16-19].

Fig 8: Injex needle free injection

4. The Future

Needle-free injections have a major drawback with a clinical concern. The high pressure delivery of drugs can damage fragile molecules beneath the skin layer, especially in the administration of monoclonal antibodies. The advances in pressure mechanism can solve the problem up to certain extent. Researchers, along with supporting

organizations like the Bill Gates and Malinda Gates Foundation, USA, are actively in pursuit of investigating methods for producing long lasting drugs that will minimize the number of needle injections, especially in the area of vaccine research.

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