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Review Paper

Needle-Free Injection Technology: A Comprehensive Review

V. Sai Muneeswari[1*], Kota. Venkata Swapna[2], Dr. Shaik Salma[3]

[1*]*Independent Researcher, Department of Pharmaceutical Analysis, Kuala Lumpur, Malaysia*
[2]*Assistant Professor, Department of Pharmacy Practice, Swathi College of Pharmacy, Nellore, Andhra Pradesh, India*
[3]*Assistant Professor, Department of Pharmacy Practice, Swathi College of Pharmacy, Nellore, Andhra Pradesh, India*

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ABSTRACT

Needle-free injection technology (NFIT) encompasses various delivery mechanisms designed to administer drugs through the skin. These systems utilize methods like Lorentz forces, shock waves, gas pressure, or electrophoresis, eliminating the need for traditional hypodermic needles. This innovation holds immense potential for both the pharmaceutical industry and public health in developing regions. It offers a safer approach to mass immunization by reducing the risks of needle-stick injuries and complications caused by reusing needles. NFIT devices are categorized by their operational principles, drug loading methods, delivery mechanisms, and application sites. Ensuring sterility, appropriate viscosity, and optimal shelf life of the drugs is crucial for delivering a safe and effective dose using NFIT. Advanced needle-free systems can effectively deliver highly viscous medications that are challenging to administer with standard needles and syringes, further demonstrating their utility. NFIT devices can be produced through multiple techniques, with injection molding being the most commonly used manufacturing process. Several versions of this technology, such as Bioject® ZetaJet™, VitaJet 3, and Tev-Tropin®, are currently available on the market. Significant investments have fueled the development of this technology, with numerous FDA-approved devices now accessible globally.

INTRODUCTION

Drug delivery via injections is a widely used method to prevent and treat various illnesses. However, this technique is invasive and may cause tissue damage. Additionally, improper handling or reuse of needles poses significant risks, including the potential spread of infectious diseases. To address challenges associated with needle-based

***Corresponding Author:** V. Sai Muneeswari
Address: *Independent Researcher, Department of Pharmaceutical Analysis, Kuala Lumpur, Malaysia.*
Email ✉: saimuniswetha2016@gmail.com

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injections, needle-free injection technologies (NFIT) have emerged as a promising alternative, gaining traction due to their numerous advantages. These innovative systems are designed to deliver drugs in both liquid formulations and solid particle dosages, offering flexibility for various medical applications. Needle-free systems provide a cutting-edge method of administering medications without the need to puncture the skin with a traditional needle. The concept of needle-free systems dates back to 1936, when Marshall Lockhart patented the jet injection. In the 1940s, researchers like Higson advanced this technology by creating high-pressure devices that used a fine liquid jet to penetrate the skin and deliver medication to underlying tissues.

Table 1: Advantages and Disadvantages of Needle Free Devices

Advantages	Disadvantages
1. Elimination of broken needles. 2. Consistent Vaccine delivery. 3. Higher antigen dispersion. 4. Elimination of worker needle sticks. 5. Elimination of needle disposal. 6. Lower pain and stress.	1. Higher start-up costs. 2. Infrastructure for exhaustible gas systems. 3. Higher requirement for training and maintenance. 4. No one size fits all NFID. 5. Worker confidence in NFID.

COMPONENTS FOR NEEDLE FREE INJECTIONS:

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

Component 1 - Injection device

The device incorporates a drug chamber and is crafted to enable self-administration. Constructed using plastic materials, it maintains sterility throughout its operation. Additionally, it includes a sterilized syringe that operates without a needle and is also made of plastic.

Component 2 - Nozzle

The nozzle functions both as the pathway for drug delivery and the surface that comes into contact with the skin. It includes an orifice through which the drug penetrates the skin during injection. Typically, the orifice diameter measures around 100 µm, enabling the drug particles to be propelled at an average speed of 100 m/s to a depth of 2 mm. A common orifice size is 0.127 mm, which is comparable to a 25-gauge needle.

Component 3 - Pressure source

Efficient drug delivery into the systemic circulation via the skin requires sufficient force. The pressure source can rely on a mechanical method, where energy is stored in a spring and released by activating a plunger to generate the required pressure. Alternatively, it can use a pressure storage system that employs compressed gas stored in a cartridge. Commonly used gases in these devices include carbon dioxide and nitrogen. The device must ensure that the pressure generated is high enough to puncture the skin while preserving the integrity of the drug molecule.

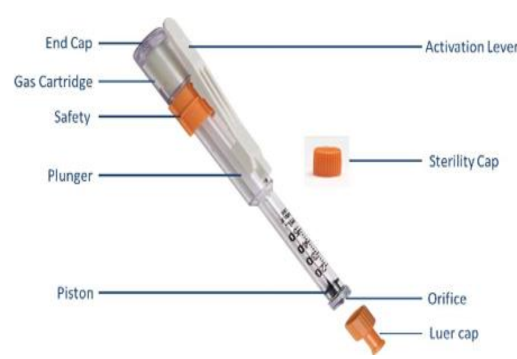

Figure 1. Components of a needle-less injection device

COMMON MECHANISM FOR NEEDLE FREE INJECTIONS:

The mechanism utilizes compressed gas, such as carbon dioxide or nitrogen, to drive the drug through an orifice at extremely high speed. During administration, an ultra-fine fluid stream penetrates the skin layers, rapidly delivering the drug into the systemic circulation. The entire injection process takes less than one-third of a second and occurs in three distinct stages:

Peak Pressure Phase: The phase where optimal pressure is applied to penetrate the skin, lasting less than 0.025 seconds.

Dispersion Phase*:* The phase in which the drug disperses, lasting approximately 0.2 seconds.

Drop-Off Phase*:* The final phase, where pressure reduces, lasting less than 0.05 seconds.

TYPES OF NEEDLE FREE INJECTION SYSTEMS

Needle-free injection drug delivery systems are classified as follows:
1. Powder injections
2. Liquid injections
3. Depot or Projectile Injection.

System Type 1 - Powder injections

- ***Design of powder injection systems***

These injections are designed with a chamber containing solid drug content and a nozzle that propels drug particles into the skin using a power source, typically compressed gas. The chamber is sealed on both sides by a diaphragm, only a few microns thick, to protect the drug content.

- ***Mechanism of powder injection***

(a) Drug particles are expelled from the nozzle alongside a stream of gas.
(b) As the particles impact the skin's surface, they create a small opening that deepens as the injection progresses.
(c) The drug particles are deposited in a spherical arrangement at the base of the opening and penetrate through the stratum corneum.
(d) Once inside, the particles spread throughout the stratum corneum and into the viable epidermis.

The powder injection process utilizes a light gas gun, which achieves the necessary particle velocity using an accelerating piston. This piston propels and carries the particles until they are released via a deceleration mechanism that slows the piston. The deceleration causes the particles to eject and target the tissue area effectively.

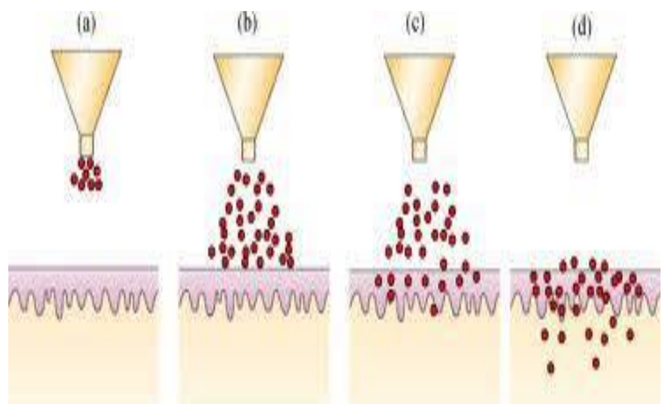

Figure 2. Mechanism of a powder injection

System Type 2 - Liquid injections

The fundamental principle behind this injection method is that if sufficient pressure is applied by a fluid in direct contact with the skin, it can create an opening in the skin and deliver the liquid into the underlying tissues. While the same principle is utilized in powder injection systems, the design and operational mechanisms differ. These devices typically incorporate components such as gas or spring-powered pistons, drug-loaded chambers, and nozzles. The nozzle in these systems generally features an orifice size ranging from 150 to 300 µm.

- ***Mechanism of liquid injections***

- The action of a piston on a liquid reservoir within a nozzle increases pressure, propelling the liquid jet out at a velocity exceeding 100 m/s.
- When the jet interacts with the skin, it initiates the formation of a hole due to mechanisms such as erosion, fracture, or other forms of structural failure in the skin.
- Continued impact of the jet causes the hole in the skin to deepen. If the rate at which the hole forms is slower than the rate at which the jet strikes the skin, some liquid may splash back toward the nozzle.
- As the hole becomes deeper, it slows the jet's penetration, leading to an accumulation of liquid inside the hole. This stagnation halts further deepening of the hole. The final dimensions of the hole are typically established within microseconds after impact. At the hole's base, the jet stagnates and causes the liquid to spread into the skin in a nearly spherical pattern.

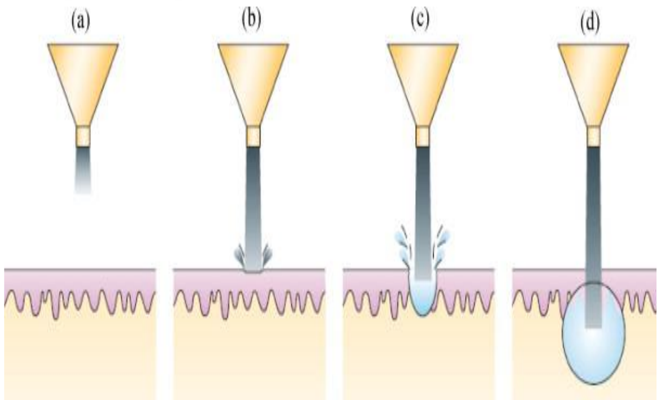

Figure 3. Mechanism of a liquid injection

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.

TYPES OF INJECTION METHODS INCLUDE:

• Spring load jet injector
• Battery powdered jet injector
• Gas powdered jet injector

Spring-Loaded Jet Injector:

This device operates through a spring mechanism that is manually drawn back. When the trigger is pressed, the spring is released, generating a high-pressure jet stream to deliver the drug via subcutaneous, intramuscular, or transdermal routes. The spring mechanism must be reset manually for subsequent uses. **Examples:** Dermojet®, Medi-jector®

Battery-Powered Jet Injector:

This system incorporates a rechargeable battery pack that powers the retraction of the dosing mechanism. It utilizes an electric piston that automatically resets after administering the dose, making it convenient for continuous use. This design resembles a battery-operated hand drill and is capable of delivering drugs subcutaneously, intramuscularly, or transdermally, depending on the recommended application. **Examples:** Intra Dermal Application of Liquids (IDAL)® by Intervet, Boxmeer

Gas-Powered Jet Injector:

This injector utilizes an air or gas cartridge connected to the device via a tubing system. Upon triggering, the compressed gas powers the piston, creating a drug jet stream for administration. It is suitable for subcutaneous, intramuscular, or transdermal drug delivery. **Examples:** Biojector®, Pulse® Needle-Free

(Felton, Lenexa, KS), Agro-Jet®/Med-Jet® (MIT, Montreal, Quebec, Canada)

ADVANCES IN NEEDLE FREE INJECTION TECHNOLOGY:

Bio-jector

Figure 4. Bio-jector needle free injection device

The Bio-jector 2000 is the sole intramuscular injection system approved by the FDA. To prevent cross-contamination, it uses disposable single-use syringes for each injection. With over 10 million injections successfully administered, there have been no reports of significant complications. This system has demonstrated its safety and effectiveness, particularly in high-risk scenarios, such as delivering medication to patients with HIV or hepatitis.

Serojet

Figure 5. Serojet needle free injection device

The Serojet device is an adaptation of Vitajet technology, specifically designed for the subcutaneous delivery of Serostim, a recombinant human growth hormone. It is utilized in the treatment of HIV-associated wasting in adults and received FDA approval for marketing in March 2001.

Cool-click

Figure 6. Cool-Click device

This device is designed for the subcutaneous delivery of Saizen, a recombinant human growth hormone. It received FDA approval in June 2000.

Intraject technology

The device resembles a pre-filled, disposable fountain pen and is designed for liquid protein formulations. Drug delivery is achieved in under 60 milliseconds by activating the actuator, which uses compressed nitrogen.

Biovalve's Mini-Ject technology

The device is user-friendly, pre-filled, and disposable. It is designed for administering large proteins, delicate antibodies, and vaccines. It supports intradermal, subcutaneous, and intramuscular delivery methods.

Antares Medi-Jector Vision technology

The device is developed for delivering insulin. It is reusable, spring-powdered and able to deliver variable doses.

Needle free, auto and pen injectors

Spring-loaded syringes are designed for single-dose administration.

Auto-injectors are widely accepted by patients due to their safety features and ease of use. Modern designs incorporate pre-filled, single-use devices that include a standard pre-filled syringe, automating needle insertion, drug delivery, and needle coverage after use. This design protects the needle tip and minimizes the risk of accidental activation.

Examples:

- **Anapens, Epipens, Twinjects:** Used for treating anaphylaxis.
- **Rebiject, Rebiject II:** Designed for multiple sclerosis treatment.
- **Sureclick Auto-injector:** Used with Enbrel or Aranesp drugs for treating rheumatoid arthritis.
- **PenInjectors:**
  These devices use pen cartridges, which can function as multi-dose vials. Patients can extract their prescribed dose using an insulin syringe and needle.

Madajet

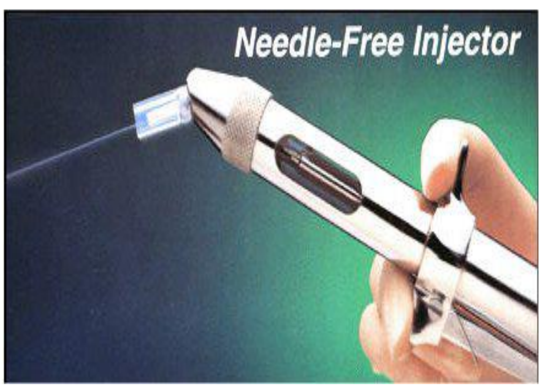

Figure 7. Madajet XL needle free injector

This injector is frequently used in dentistry, relying on pneumatic pressure to deliver local anesthetic. The drug formulation is discharged as a fine stream that penetrates 4 to 5.5 mm beneath the skin's epithelium. At the injection site, the stream forms a wheal approximately 5 to 6 mm in diameter. The device administers 0.1 cc of the anesthetic per intra-dermal injection.

Bioject ®- Zetajet

Figure 8. Bioject ®- Zetajet

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.

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.

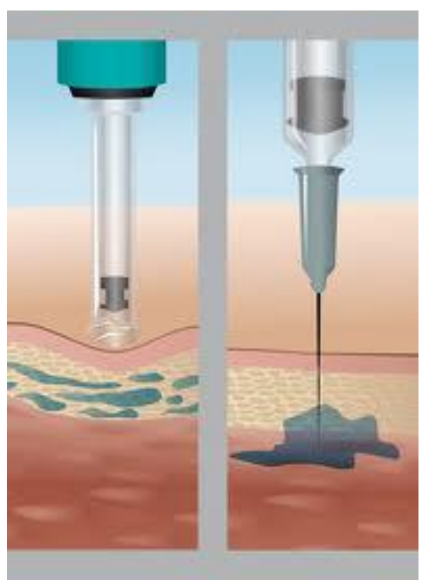

Figure 10. Injex needle free injection

THE FUTURE

Needle-free injection systems offer numerous advantages; however, they present certain challenges, particularly concerning the delivery of delicate molecules like monoclonal antibodies. The high-pressure mechanism employed to penetrate the skin can potentially compromise the integrity of these sensitive compounds. To address this issue, advancements in pressure modulation are being explored to ensure the safe administration of such therapeutics.

In parallel, organizations such as the Bill & Melinda Gates Foundation are actively supporting research aimed at developing long-acting drug formulations. These innovations are designed to reduce the frequency of injections, thereby enhancing patient compliance and comfort. A significant focus of this research is in the field of vaccine development, where extended-release formulations could revolutionize preventive healthcare by minimizing the need for multiple doses.

MARKETED PRODUCTS:

Table 3: Needleless Injection Devices on Market

Product	Company	Actuation method	Depth of penetration	Drug types	Drug volume(ml)	Comments
Biojector 2000	Bioject	Compressed gas	Intra-muscular, subcutaneous	Liquid	1ml.	Used to deliver vaccines
Vitajet 3	Bioject	spring	Subcutaneous	Insulin	0.02-0.5	Can be self administered
Iject	Bioject	Compressed gas	Intra-muscular, subcutaneous, Intra-dermal	Liquid	variable	Available for single use or multiple use
Injex30	Injex	spring	Subcutaneous	Insulin	0.05-0.3	Dual safety systems is present
Injex50	Injex	spring	Subcutaneous	Insulin	0.1-0.5	Deliver larger dose than injex30
Injex 0	Injex	spring	Subcutaneous	Insulin	0.8-1.5	Deliver largest dose among injex products
Medi-Jector Vision	Antares	spring	Subcutaneous	Insulin	-----------	Compatible with all types of U-100 insulin
Intraject	Aradigm	Compressed gas	Subcutaneous	Liquid	0.5	Deliver drug in less than 60 milli sec
Miniject	Bio-Valve	Compressed gas	Intra-muscular, subcutaneous, Intra-dermal	Liquid	0.1-0.3	Can deliver wide range of drugs
Crossject	Crossject	spring	Intra-muscular, subcutaneous, Intra-dermal	Liquid	0.2-1	Operating based on novel gas tech
Penject	Penject	Compressed gas	Intra-muscular, subcutaneous, Intra-dermal	Liquid	0.1-0.5	Low cost, easy to operate

CONCLUSION

"Needle-free injectors offer a range of benefits, including enhanced reliability, user-friendliness, efficiency, and safety, without the complications of needle disposal. With increasing patient acceptance, ongoing innovations, and reducing costs, these systems are becoming a preferred option for vaccinations and insulin treatments. The outlook for needle-free injection systems is promising, supported by the growing need to prevent needle-stick injuries and to provide pain-free medication delivery. This positive trend is reinforced by robust clinical trial data. Key applications poised to drive the success of these technologies include vaccine administration, delivery of biotechnology drugs like proteins and peptides, gene therapies, and insulin management. Over the years, needle-free devices have evolved significantly and are expected to play a pivotal role in the future of drug delivery technologies.

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