Review Article

Review on Needle Free Drug Delivery Systems

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ABSTRACT

Needle-free liquid jet injectors have been used for more than 50 years for parenteral delivery of vaccines and drugs. Although excellent bioavailability has been reported for a number of drugs, occasional pain and bruising have limited wide acceptance of jet injectors. This article reviews jet injectors with respect to their current clinical applications, emerging applications, mechanistic understanding and future prospects. The researchers say that among other benefits, the technology may help reduce the potential for needle-stick injuries; the Centers for Disease Control and Prevention estimates that hospital-based health care workers accidentally prick themselves with needles 385,000 times each year. A needleless device may also help improve compliance among patients who might otherwise avoid the discomfort of regularly injecting themselves with drugs. A needleless device may also help improve compliance among patients who might otherwise avoid the discomfort of regularly injecting themselves with drugs. This narrative review aims to discuss about the needle less injection, their applications and advantages over needle injections. A comprehensive and thorough literature review was done about needle free injections technologies and needle free injection devices currently available on the market and the information regarding it was clearly placed in this article. The main drawbacks of needle injections that prompt scientists to look for the needle less injections were explained. An overview of recent trends and other needleless drug delivery systems was also explained.

Keywords: Microjets, needle free devices, needleless injection, powder jets, pulsed microjets, shock waves.

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INTRODUCTION

Drug delivery plays a pivotal role in the field of human health care where nearly 12 billion injections are administered annually for medical purposes, 3% of which are used for immunization. Throughout the world, 0.7% of deaths and 0.6% of disability-adjusted life years (DALYs) are caused by contaminated injections in health care settings. In low- and middle-income countries, the possibility of HIV transmission through contaminated injections is high. Each year, unsafe injections cause an estimated 1.3 million early deaths, loss of 26 million years of life, and an annual burden of $535 million (U.S. dollars) in direct medical expenses. Apart from the unsafe injections, needle injuries, accidental needle sticks, needle phobia, and possible side effects due to transiently high plasma drug concentration are very common. A needle-free delivery system that can deliver the drug either actively or passively is a rational alternative. In the case of delivering the drug actively, a driving force is necessary for the transport of drug across the skin, which may be accomplished using jet injectors, electroporation, iontophoresis, ultrasound, powder injection, and tape stripping. Different delivery systems have been developed to deliver vaccine to the epidermal layer of skin [1].

HISTORY

Needles are painful due to their thickness, which is mostly required for structural reasons .The first air-powered needle-free injection systems were developed during the 1940s and 1950s for mass administration of vaccines to US soldiers. These first injectors used compressed gas to propel milliliters of liquid into the skin, even into muscle. These devices were gun-shaped and used propellant gases to force fluid medicines through the skin. The obvious benefit of this research is to eliminate pain from injections. Today, there are commercially available jet injectors that derive from these military prototypes, like the Biojector from Bioject Inc [2, 3].

Needle injection of drugs is one of the most invasive methods of drug administering, it damages the tissue which may not heal in case of patients with diabetes, and in case of careless injection a patient can die from administering tiny bubble of air into a vein, infection or inflammation, it also is painful if performed improperly, also it is very hard to control the amount of drug administered by an injection and can cause an overdose and in some cases death.

Needle although effective has several draw backs.

- Needles are expensive. The cost results in a lower vaccination rate, especially for children in developing countries.
- Lack of reusability, if a needle syringe is not sterilized reusing it can lead to the spread of disease.
- Many people have a fear of needles (often called Trypanophobia, Belonephobia or Aichmophobia) which causes them to avoid treatment. Needle phobia affects at least 10% of the general population.
- Accidental needle sticks lead to injuries and possible infections [2].

Advantages and disadvantages for needle free devices shown in (**Table 1**).

Table 1: Advantage and Disadvantages of Needle-Free Devices [4]

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

Needle-Free Technology: Origin and Methodology

Needle-free technology, first called jet injectors, were developed in the 1930s and used mass vaccination programs in people for smallpox, polio, and measles. Using mechanical compression to force fluid through a small orifice, these devices produced a high-pressure stream that could penetrate skin and subcutaneous tissue to deliver the vaccine. Most of the older devices used the same nozzle faces and fluid pathways to dose all the individuals; thereby causing potential safety hazards of transferring blood-borne pathogens between individuals.

While hypodermic needles were first introduced during the 1800s, needle-free systems are relatively recent inventions. The needle-free systems that are most like traditional injections involve the direct transfer of the medicine through the skin. Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. Needle-free injection devices propel a small jet of liquid or powder at high speed, causing it to penetrate the skin for subcutaneous, intradermal, or intramuscular administration. These devices have been used for mass vaccinations for a number of years; however, only recently they are being promoted as devices for the self-administration of parenteral drugs. 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 a needle [4].

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 ultra-fine stream of fluid penetrates the skin, delivering the vaccine in a fraction of a second to the skin, subcutaneous tissue, and underlying shallow muscle. Components for needle less injection shown in (**Fig. 1**).

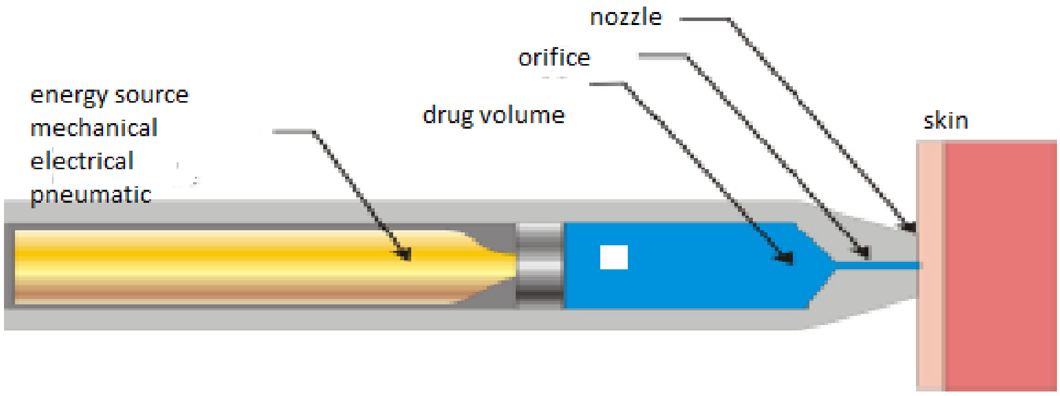

Fig 1: Components for Needle Less Injection

Nozzle: The nozzle has two critical 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. A comparison of relative diameters for a 24 Gauge (diameter of 460μm) needle, a 100 mm injection stream and a human hair. From this figure it is seen that the needle-less stream is much smaller than the average injection needle.

Drug reservoir: The drug volume holds the injection fluid inside the device.

Pressure source: The energy source provides the necessary driving energy to the drug for injection. Many of the devices on the market use either mechanical or stored pressure as energy storage elements. The mechanical method stores energy in a spring which is released pushing a plunger to provide the necessary pressure. The pressure storage method uses com-pressed gas in a vessel which is released at the time of injection [2]. Mechanism of working of device is shown in (**Fig. 2**).

Mechanism of working of device

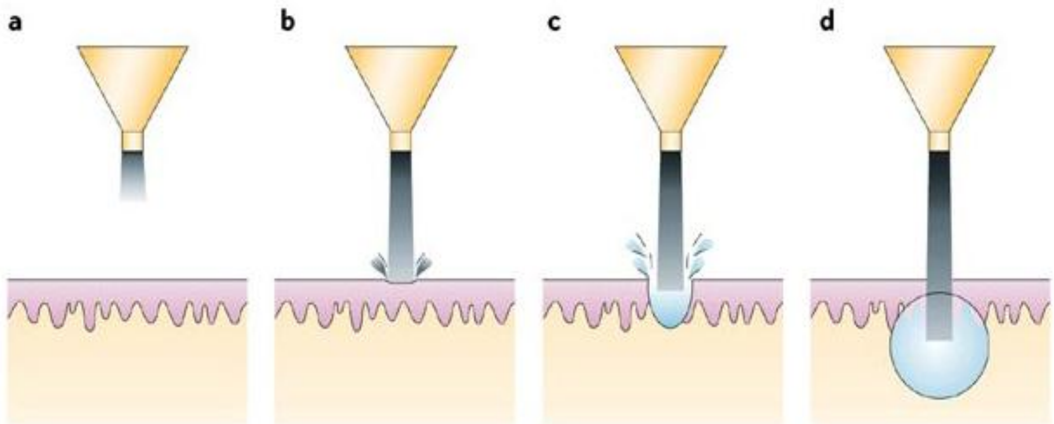

Figure 2: Transdermal Injections (Visualizing the Process)

A) 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 > 100 m/s).

B) Impact of the jet on the skin surface initiates formation of a hole in the skin through erosion, fracture, or other skin failure modes.
C) Continued 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.
D) As the hole in the skin becomes deeper, the liquid that has accumulated in the hole slows down the incoming jet, and the progression of the hole in to the skin 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 [4].
Needle-free technologies can be broadly separated into three types:
1. Powder injections,
2. Liquid injections,
3. Depot (or projectile) injections.

Powder injections

Systems are powered by a manufactured helium gas aluminum micro-cylinder of ampoule design and use a drug cassette or package to introduce the powder into the gas flow. In operation, the micro-cylinder tip can be broken when the device is pressed against the tissue site to be treated. This releases the compressed helium suddenly to open the drug cassette for delivery of its payload to the tissue. The gas does not actually penetrate the skin, instead, it is reflected back in to the device through a silencer. The silencer is necessary because the flow is transiently supersonic. The other components of the device are manufactured from medical grade plastics using standard injection molding techniques.

Liquid injections

The basic principle of this injection is "if a high enough pressure can be generated by a fluid in intimate con-tact with the skin, and 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 but there is difference in the actual design and operation of the powder injection devices.

Depot injections

Depot injections are given in the muscle, where they create a store of a drug that is released continuously over a specified period of time [1].

Advantages of NFI technology

1. Avoid real as well as needle phobia based pain.
2. Obviate needle stick hazard and sharps disposal.
3. Enhance stability by ambient storage and delivery as a dry powder.
4. Eliminate complexity of reconstitution and any effects of shear.
5. Provide rapid delivery and reproducibility comparable with needle and syringe.
6. Improve bioavailability over other none or less invasive drug delivery systems.
7. Improve immune response to DNA and conventional vaccines.
8. Provide the capability to alter the pharmacokinetics of certain drugs.
9. Jet injectors are used to deliver mass immunization of influenza, tetanus, typhoid, diphtheria,

Pertussis and hepatitis a vaccines. Needle-free injection devices can even classified into 2 types based on the source of power:
1. Spring-powered
2. Compressed gas powered [4].

Spring-powered devices 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. Needle-Free injectors used with animal health products listed in (**Table 2**).

Table 2: Needle-Free Injectors Used With Animal Health Products [4-6]

Type of needle-free device	Brand Name/Manufacturer
Spring-loaded	DERMOJET®/VACCI-Jet Société AKRA, France MEDI-JECTOR®-Antares Pharma, Ewing, NJ

Battery-powered jet injector	Intra Dermal Application of Liquids (IDAL) ®- Intervet, Boxmeer, The Netherlands
Gas-powered jet injectors	BIOJECTOR® -Bioject, Tualatin, OR PULSE® Needle-Free - Felton, Lenexa, KS

Marketed Products

Needleless Injection Devices On Market listed in (**Table 3**)

Product	Company	Actuation method	Depth of penetration	Drug types	Drug volume(ml)	Comments
Biojector 2000	Bioject	Compressed gas	Intramuscular,sub cutaneous	Liquid	1ml.	Used to deliver vaccines
Vitajet 3	Bioject	spring	Subcutaneous	Insulin	0.02-0.5	Can be self administered
Iject	Bioject	Compressed gas	Intramuscular,sub cutaneous, Intradermal	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 injex 30
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	Intramuscular,sub cutaneous, Intradermal	Liquid	0.1-0.3	Can deliver wide range of drugs
Crossject	Crossject	spring	Intramuscular,sub cutaneous, Intradermal	Liquid	0.2-1	Operating based on novel gas tech
Penject	Penject	Compressed gas	Intramuscular,sub cutaneous, Intradermal	Liquid	0.1-0.5	Low cost ,easy to operate

Table 3: Needleless Injection Devices on Market [1]

Recent Trends:

Pulsed micro jets: Despite their long history, needle-free liquid jet injectors are not commonly used as a result of frequent pain and bruising. It was hypothesized that pain and bruising originate from deep penetration of jets into skin leading to their interactions with nerves and blood capillaries. This issue could potentially be addressed by minimizing the penetration depth of jets into the skin; however, attempts to reduce the penetration depth have led to a concurrent loss of delivery efficiency .This issue was solved when a new strategy came into existences that are pulsed micro jets [7].

Microjets were produced by displacing the drug solution through a micro nozzle (50–100 m in final diameter) by using a piezoelectric transducer. Other modes of fluid displacement, including dielectric breakdown and electromagnetic displacement, can also be potentially used however; the piezoelectric-based mechanism was preferred as a result of its robustness and energy efficiency. The piezoelectric transducer, on application of a voltage pulse, expands rapidly to push a plunger that ejects the fluid from the micro nozzle as a high speed micro jet. The volume of the micro jet is proportional to the amplitude of the voltage pulse measured with a colorimetric assay) and the velocity of the micro jet is proportional to the rise time The high-velocity of micro jets (*v* _100 m/s) ensures skin penetration but small jet diameters (50–100μm) and extremely small volumes (a few nanoliters) limit the penetration depth. Pulsed micro jet injectors could be used to deliver drugs for local as well as systemic applications without using needles. Comparative study between Micro jets injector and conventional jet injector discussed in (**Fig. 3**).

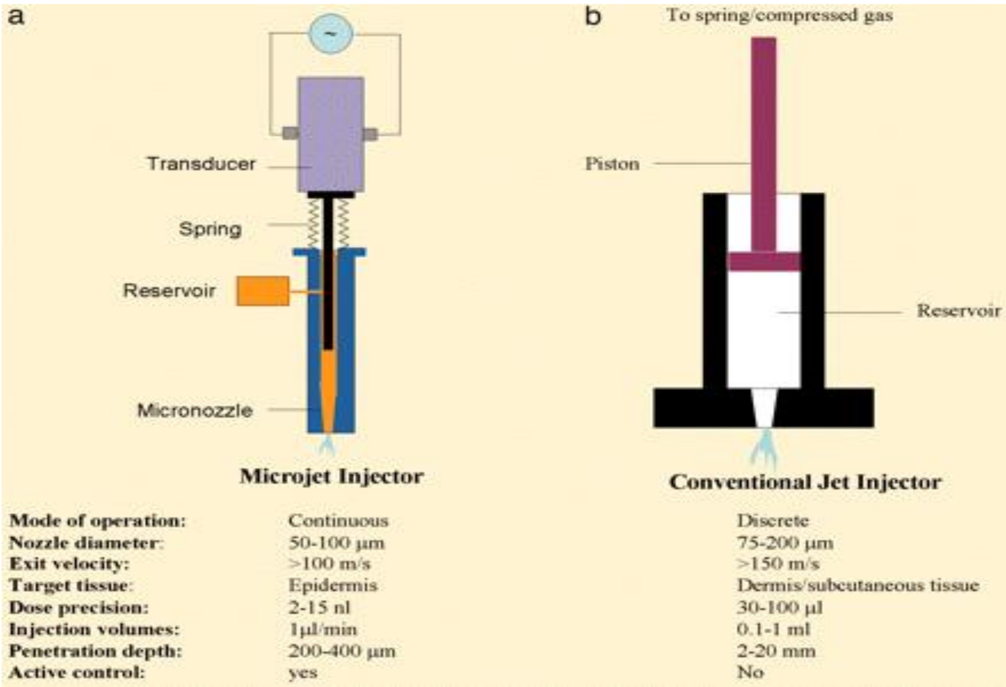

Figure 3: Micro Jet Injectors V/S Conventional Jet Injectors [8]

Shock waves: The most efficient mechanisms of energy dissipation observed in nature. In this study, utilizing the instantaneous mechanical impulse generated behind a micro-shock wave during a controlled explosion, a novel nonintrusive needleless vaccine delivery system has been developed. It is well-known that antigens in the epidermis are efficiently presented by resident Langerhans cells, eliciting the requisite immune response, making them a good target for vaccine delivery. Unfortunately, needle-free devices for epidermal delivery have inherent problems from the perspective of the safety and comfort of the patient [9, 10]. The penetration depth of less than 100 μm in the skin can elicit higher immune response without any pain. Here we show the efficient utilization of our needleless device (that uses micro-shock waves) for vaccination. The production of liquid jet was confirmed by high-speed microscopy, and the penetration in acrylamide gel and mouse skin was observed by confocal microscopy. *Salmonella enterica* serovar, Typhimurium vaccine strain pmrG-HM-D (DV-STM-07) was delivered using our device in the murine salmonellosis model, and the effectiveness of the delivery system for vaccination was compared with other routes of vaccination. Vaccination using our device elicits better protection and an IgG response even at a lower vaccine dose (10-fold less) compared to other routes of vaccination [3].

CONCLUSION

Needle Free Injectors are more reliable, easier to use, more efficient, much safer and have no disposal problems. Acceptance by patients, continuing developments and lowering costs all make needle free systems the best method for vaccinations, insulin self treatments. The future of needle-free injection systems looks bright, with a steady growth due to increasing demand for prevention of needle stick injuries and painless delivery of medication and this fact is further strengthened by the strong clinical trial data available. Some of the applications expected to be key to the success of needle-free technologies include vaccines, biotechnology drugs - protein and peptide delivery, gene delivery, and insulin. Needle-free devices have come a long way to the present state and are expected to play an increasingly important role in the novel drug delivery technologies markets in the coming years.

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