Research Article

Needleless Injection System

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ABSTRACT
Even though oral route is the most preferred one, certain conditions necessitate the use of parenteral dosage form. But this route being invasive, is considered as non-patient compliant. Thus, there came a need for a more patient compliant system which led to the development of needleless injection technology. This review intends to throw light on the basic mechanisms by which this technology works, its applications and thereby also discusses the scope it has for the delivery of many new upcoming drugs.

Keywords: patient compliant, needleless injection technology, basic mechanisms, applications.

INTRODUCTION
The most convenient and patient compliant dosage form is oral but in certain conditions like the need for immediate action or stability, parenteral route needs to be used. There are a variety of problems with the use of hypodermic needles for injections. One of the most significant being the pain associated with it.
Needle-free systems are designed to solve these problems making them safer, patient-compliant and more convenient. A major objective of these systems is to increase the incidence of vaccination and reduce the amount of prescribed antibiotics.[1] Needleless injection systems are gaining importance especially for vaccines due to pandemic disease, bioterrorism, and disease eradication campaigns.[2] The needle-free injectors are the devices that deliver drugs (mostly vaccines) through an orifice with a high-speed and thus producing a fine stream of medication. Even though the skin is punctured in this technique similar to that of a needle system, the diameter of the stream is much smaller than a conventional needle and so it produces less pain that is no worse than a mosquito bite. [3] The needle-free devices come in different designs with a variety of options for power sources.

HISTORY
Scientists in the past took many efforts to develop various alternatives to hypodermic needles. Transdermal patches were one among them but it was seen that only small molecules could penetrate the skin and so its use was limited.
With discovery of newer larger moieties, it became necessary to come up with newer technologies for delivering them.[4]

First came the spring based needle free technology and later came the air-powered needle-free injection systems during 1940s. These devices were gun-shaped and used propellant gases like nitrogen or helium to force fluid medicines through the skin. Over the years, the devices have been modified for greater ease of use.[1]
Earlier used jet injectors were multi-use devices that delivered vaccine through the same nozzle for multiple patients and are referred to as 'multi use-nozzle jet injectors'.[5] More recently single-use-nozzle devices are employed which uses disposable cartridges of vaccine. This type facilitates a non-reusable fluid path and nozzle for each patient, and is referred to as a 'disposable cartridge jet injector'.[6,7]

RAW MATERIALS
They must be made from materials that are pharmacologically inert since these devices come directly in contact with the body. As the materials are heat sterilized, they must also be able to withstand high temperatures. The outer shell of the device is made from a high strength and light-weight thermoplastic like polycarbonate. Fillers are added to make polymers easier to mold and to produce more durable, light-weight and rigid plastics. Colorants are also incorporated into the plastic to improve the appearance. Plastics, for manufacturing, are supplied in pellet form with the colorants and fillers already incorporated into it.[1]

DESIGN
All needle-less injection systems have three basic components in common which includes a nozzle, drug reservoir and a pressure source. The nozzle comes in direct contact

with the skin and has an orifice through which the drug passes. The energy source provides the necessary driving force for injection. Fig.1 shows the basic layout of a needle-less injection device.[8]

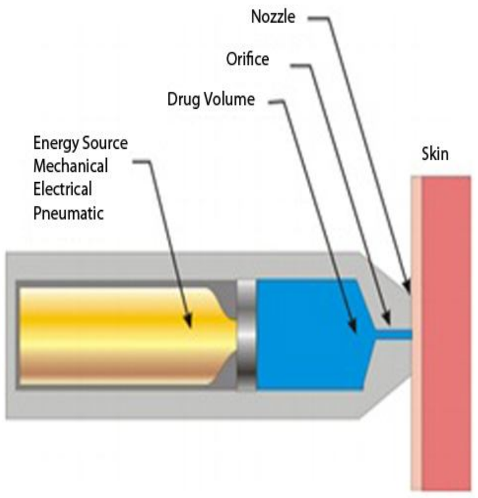

Fig. 1: Basic components of most needle-less injection systems

MECHANISM

In a needle-less injection system, the drug stream is forced out with a high pressure using appropriate energy sources. This pressure is localized at a point on the skin surface which punctures the skin and delivers the drug in a fraction of a second to the desired site. The pressure profiles can be altered to make the drug reach a particular site by controlling the power source and this is the beauty of the device.

A comparison of relative diameters for a 24 gauge (diameter of 460 µm) needle, a 100 mm injection stream and a human hair is shown in the Fig.2. From this figure, it is seen that the needle-less stream is much smaller than the average conventional injection needle.[8]

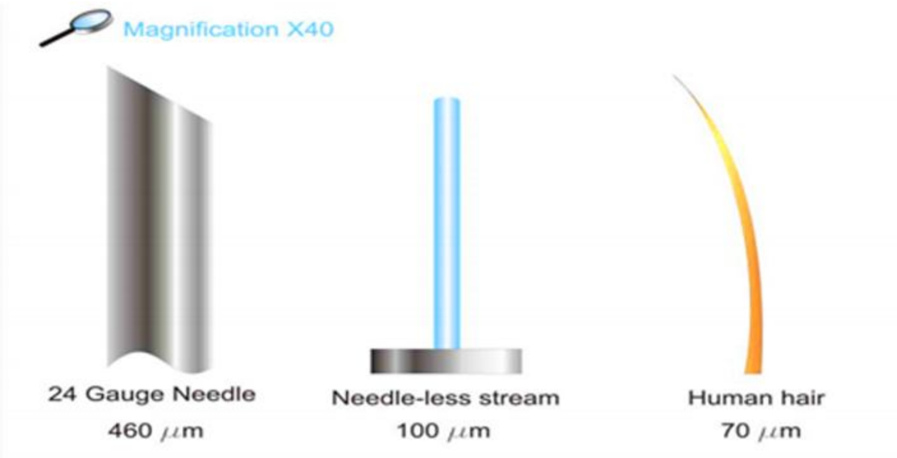

Fig. 2: Size comparison of a human hair, 24 gauge needle and drug stream

TYPES OF NEEDLELESS INJECTION SYSTEM

There are several types of needleless injection system based on the mechanism of providing the necessary energy like jet injectors based on high pressure of compressed gas, spring loaded systems, shape memory actuation etc. Some of these are discussed below:

1. Jet injectors based on air pressure

This jet injector uses a high pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis. It is powered by compressed air or gas supplied either by a pressure hose from a large cylinder or from a built-in gas cartridge or small cylinder. The first needle-free jet injector was patented in 1960 by Aaron Ismach. It was used to administer vaccinations for smallpox and other infectious diseases. Assisted by Dr. Abram Beneson, Ismach created two different types of jet injectors – the foot-powered injector or Ped-O-Jet and the jet injector gun.[9]

2. Magnet based system

MIT (Massachusetts Institute of Technology) researchers have developed a jet injector that uses a Lorentz-force (electromagnetic force) actuator that propels fluid at a speed close to that of sound. The actuator is a tiny, powerful magnet surrounded by a coil of wire which is attached to a piston inside the drug vial. When the current is applied, this force propels the formulation through a nozzle as small as a mosquito's stinger.

It has been reported that the velocity can be modified by the amount of current used and thus creating waveforms in two phases. The initial high-pressure phase ejects the drug at a high-enough velocity to puncture the skin and reach the desired depth. This is followed by a low-pressure phase where the drug is delivered in a slower stream that facilitates easy absorption by the surrounding tissue.[4] Fig.3 shows MIT-engineered magnet based needle free injection system.

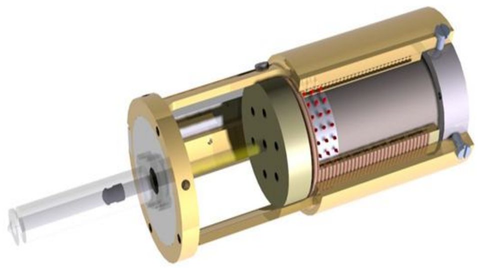

Fig. 3: MIT-engineered magnet based needle free injection system

3. Spring based system

This system employs a re-usable spring to activate a single-use high-velocity mechanical plunger. This mechanical method stores energy in a spring which is released by pushing a plunger to provide the necessary pressure. Each time the spring-load is activated, the spring must then be manually redrawn to be used for the next time.

Spring-powered devices have the advantage of being compact and of lower cost but they have a limited range of forces and versatility and so have been used primarily for subcutaneous administration of drugs.[10]

4. Laser-powered system

This type of injector has two chambers separated by a thin and flexible membrane. One chamber contains water that acts as the "driving" fluid and the other holds the drug. Each laser pulse which lasts for just milliseconds creates a bubble in the water which in turn creates pressure on the drug-filled chamber causing the medication to eject out.

The type of laser is that which is mostly used by dermatologists for cosmetic skin treatments. The high-light of this device over a piston-like mechanical injector is that the laser provides more precise dose control.[11]

5. Shape memory actuation system

Shape memory alloy has an ability to generate high stresses and has unique contractile properties that has been used as a method of actuation for a needle-less injection system. One example of the shape memory alloy is the nickel-titanium (NiTi) alloy used in the form of a wire which contracts when heated. Fig. 4 gives an idea about assembly of NiTi wires in shape memory actuation system.

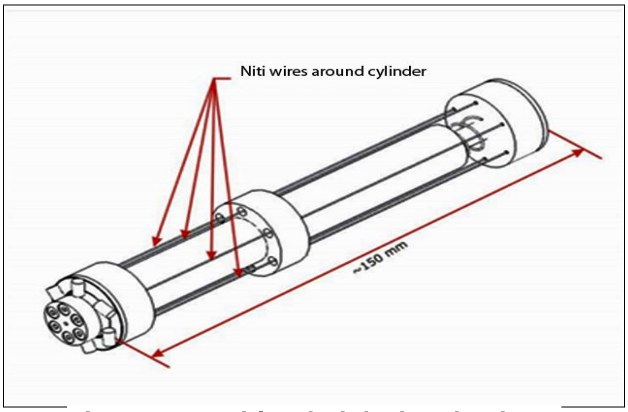

Fig. 4: Assembly of NiTi wires in shape memory actuation system

The principle behind this is that the alloy undergoes a phase transition when it is heated and gets transformed into a phase that is more stiffer and thus the NiTi wire decreases in length and increases in width. This provides the driving force for the actuation by pulling the cylinder and ejecting the drug out.[8] Model of shape memory actuation system is shown in fig.5.

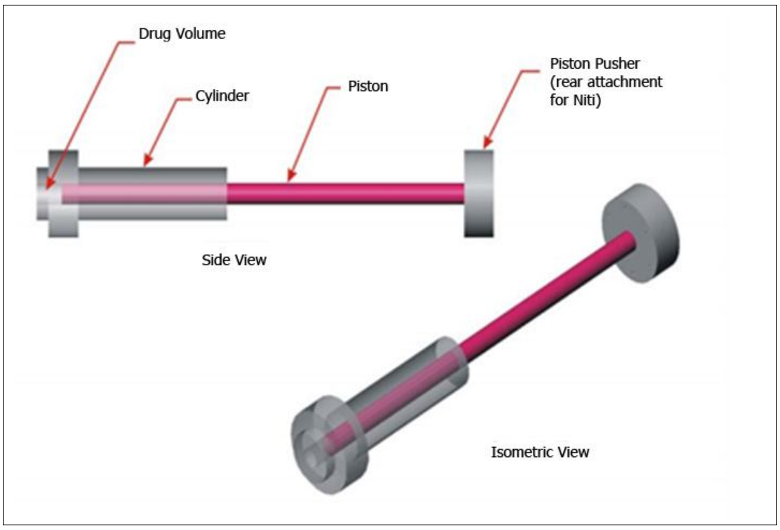

Fig. 5: Model of shape memory actuation system

THE MANUFACTURING PROCESS

The manufacturing process involves molding the pieces, assembling them and labeling the final product. The individual pieces are typically produced off-site and is then assembled by the needle free injection system manufacturer. All the processes are done under sterile conditions.

Production of components

The first step includes the production of plastic components from plastic pellets by a process called injection molding. Firstly, pellets of plastic are heated to make them flowable. The molten mass is then passed into the mold through a hydraulically controlled screw. The mold is made up of two metal halves that form the shape of the part when brought together. The plastic mass is held under pressure for a specified amount of time and then gradually allowed to cool to harden the plastic. After the plastic parts are ejected from the mold, they are manually inspected to remove damaged parts.

Assembling and labeling

The parts are next transported to an assembly line where calibrated machines apply precise markings to show dose levels. Depending on the complexity of the device, human workers are employed or machines may be used to assemble the devices. This assembling involves inserting various pieces into the main housing and attaching any buttons.

Packaging

After assembling, the devices are wrapped in sterile films and then put into cardboard or plastic boxes. Each part is packaged so as to minimize the movement and thereby the damage. For consumer products, an instruction manual is inserted for directions for use along with safety information.

EVALUATION

Line inspectors check the plastic components throughout the manufacturing process to assure conformance to predetermined specifications. Primary checking is done by visual inspections but machines are also used to check the dimensions including size and thickness. Instruments that can be used include laser micrometers, calipers and microscopes. Inspectors also check the printing and labeling.[1]

A drug velocity experiment can be conducted using a break beam module which relates directly to injection depth. The schematic of break-beam set-up is shown in fig.6.

The break beam module measures the time for a stream of drug to travel a known distance. The break beam sensors are supplied with a voltage and as the beam passes through each break beam sensor, a pulse is recorded by the voltage change that occurs. By dividing the distance by the time difference between the two pulses, the average velocity can be found.[8]

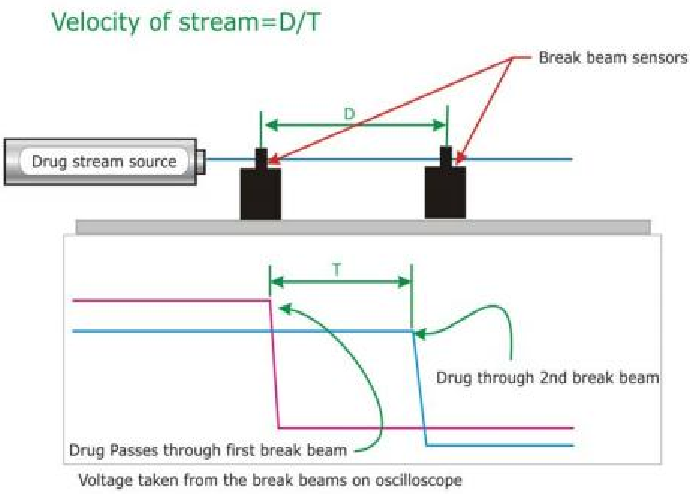

Fig. 6: Schematic of break beam set-up

VARIOUS PHYSICAL FORMS OF INJECTABLE FORMULATIONS

Apart from using liquid formulations for injections, the following forms can also be used

1. Powder Needle-Free Injection

Particles of sufficient density and particle size are accelerated to a sufficient velocity to penetrate the skin in large numbers so as to produce a therapeutic dose.

There are two different ways of formulating the drug:

a) In the first case, the drug (pure or sometimes with excipients) is presented as hard particles of 10–50 mm in diameter with a density approximately same as the crystalline drug.
b) In the second case (mostly used for vaccines), the drug is coated onto gold spheres of a few micrometers in diameter. The gold particles act as a vector for the vaccine, penetrating the stratum corneum and then often the cell membrane in case of a DNA vaccine to enable the DNA to be taken up by the cell nucleus.

But it has a limitation that it is difficult to accurately predict the proportion of a dose that is delivered into the epidermis since not many particles have sufficient momentum to travel through the epidermis into the dermis. Also, the maximum possible payload is only about few mg. Therefore, this technology is suited for only those drugs with an effective dose of 1 mg or less where accurate dose titration is not required and where epidermal delivery is advantageous.

2. Depot Needle-Free Injection
This is a new technology where the drug is formulated into a long and thin depot with sufficient mechanical robustness. This tip is formed from the formulation itself or from a soluble inert material such as sugar. The depot needs either to be manufactured aseptically or terminally sterilized. Sufficient force is exerted to penetrate this depot deep into the skin. The depot formed is usually about 1mm in diameter and a few mm long and so this is suitable only for drugs with a low dose like therapeutic proteins and antibodies. Dose can be varied by manufacturing depots of different lengths.

RECENT NEEDLE-FREE INJECTION TECHNOLOGIES
The technologies and the companies behind them that are currently active in this field are:

Algorx
Algorx has the rights to develop a helium powered device i.e. PowderJect needle-free injection technology in all areas except DNA vaccines.[12] ALGRX 3268 and ALGRX 4975 are in clinical trials. ALGRX 4975 (capsaicin for injection) is being developed especially for severe postsurgical pain, post-trauma neuropathic pain and musculoskeletal pain (including osteoarthritis and tendonitis).[13]

Antares
Antares develop metallic spring powered devices.[12] It has a collaborated product with Tjet® device which offers injections of TEV-TROPIN® (Somatropin).This device is only compatible with TEV-TROPIN® brand of human growth hormone.[14]

Aradigm
Aradigm has recently acquired Intraject technology from Weston Medical which is a compressed nitrogen gas powered, single use, prefilled, disposable system. Aradigm uses Intraject technology in collaboration with Roche for the delivery of pegylated interferon alpha (Pegasys) and GlaxoSmithKline for Imitrex (Sumatriptan).

BioJect
BioJect has its products-Biojector and Vitaject which are well known in the market for several years. These are reusable devices powered by either compressed carbon dioxide or by metal springs. In addition, BioJect is developing Iject- a prefilled, disposable device.[12]

BioValve
BioValve has developed a disposable device MiniJect which is powered by a proprietary chemical gas generation system.

Caretek Medical
Caretek developed a solid form of the drug Sumatriptan Succinate for migraine which is meant for depot needle-free delivery system to be injected using the company's patented ImplaJect device.[15]

Cross-Ject
Cross-Ject has developed a system based on airbag gas generation technology.

National Medical Products
National Medical Products (NMP) developed a disposable needle-free injector, the J-Tip, powered by a charge of carbon dioxide gas.

PowderMed
PowderMed has recently acquired the rights to Powder- Ject which is a powder needle-free technology.

Visionary Medical Products
The PenJet system, developed by VMPC, is a single-use, disposable device powered by compressed gas and uses a prefilled, polycarbonate cartridge.

ADVANTAGES
The advantages of needleless injection system are as follows:

1. There are no chances of under- or overdosing.
2. It is especially useful in case of patients with needle phobia (up to 15% of people are clinically needle-phobic “Belenophobics”).
3. It delivers pain-free injection.
4. Good patient compliance leading to effective treatment especially in cases where chronic administration is needed.
5. Avoids the need to visit hospitals for injections.
6. There are no specific disposal requirements.
7. There is no risk of cross-contamination from needle-stick injury.[12]
8. Since the force of delivering the medication can be controlled, the amount of medicine delivered and the depth can be adjusted.
9. Vaccines, which are mostly in liquid form, needs to be refrigerated if they

are to be delivered to the developing countries. In case of break-down of coolers, the whole batch gets spoilt. This can be prevented if vaccines are delivered in powdered form which is possible by using needleless injection technology.[16-17]

10. Vaccines delivered by needleless systems get dispersed more uniformly in the tissues which enable better contact of vaccine antigen with the immune cells to produce enhanced immune responses.
11. Viscous liquids can be delivered with ease using this technology.

APPLICATIONS

The following are the drugs which are widely used with this technology.

1. Insulin, which is to be administered several times during the day is considered to be the best candidate for needleless delivery.
2. Lidocaine hydrochloride, a local anesthetic is suitable to be delivered needle free.
3. Fentanyl (an opioid analgesic), Heparin (an anticoagulant) and a variety of vaccines are delivered using this system.

This technology has been tried with several newer drugs to delivery them in a patient compliant way and has been successful in most cases.[1]

CONCLUSION

Due to the pain-free nature of the technology, this has got the potential to replace all current needle systems to make parenteral route more patient compliant. Researchers are planning to broaden its field of application to be one day used for microsurgery, delivering drugs for arthritis to sensitive joints and even for pain free tattooing.

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