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NEEDLELESS INJECTION SYSTEM: AN OVERVIEW

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ABSTRACT

Needle-less injections are designed to solve the problem associated with hypodermic needle injection. Needle-less injection system was first introduced by Marshell Lockhart in1936. Needle-less system is based on the principle of electrophoresis to deliver the medicament through the skin. This devices are easy to use, it does not required any skilled person. This review is inclined on the needle-less injection system which gives detail information about advantages, disadvantages of the system. This review 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. This review also gives brief knowledge about the components. This review also gives brief information about injection methods i. e. spring load jet injector, battery powdered jet injector, and gas powdered jet injector.

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INTRODUCTION

Oral route is the most convenient for the patient but for immediate action or stability, parentral 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. Needle-free injection systems are novel ways to introduce various medicines into patients without penetrating the skin with a conventional needle. Needle-free systems were first described by Marshall Lockhart in 1936. Then in the early 1940's Higson and others developed high pressure "guns" using a fine jet of liquid to penetrate the skin and deposit the drug in underlying tissue. [1, 2].

The needle-free injectors are the devices that deliver drugs (mostly vaccines) through an aperture with a high-speed and thus producing a fine stream of medication. This creates an ultra-fine stream of high-pressure fluid that penetrates the skin without the use of a needle. 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.

This technology is used to deliver not only drugs but also proteins, peptides, monoclonal antibodies, small molecules and vaccines. Now days, This become more safer method and increases patient compliance. [3]

Objective:

The main objective of needleless injection is:

1. To avoid the risks and complications involved in conventional needles and to be used in diseases like diabetes, skin disease, allergy, asthma, etc. as a drug delivery system.
2. To avoid the drawbacks of needle injection such as anxiety, fear.

Advantages:

1.Prevent skin puncture hazards and its destruction;also does not cause problem of bleeding or bruisingand minimal skin response.
2. Avoid real as well as needle phobia based pain.
3. Provide rapid delivery and reproducibility comparable with needle & syringe.
4. Improve bioavailability over other non- or less invasive drug delivery systems.
5. Improve immune response to DNA and conventional vaccines.
6. Provide the capability to alter the pharmacokinetics of certain drugs.
7. It is trouble free, simple and self-administered.
8. Low sensation and safety.
9. Solid dosage forms can be administered.
10. Minimal skin response and no bleeding or bruising.
11. Excellent dose response is observed with increased drug doses.
12. Bio-equivalence has been demonstrated enabling the development of generic drugproteins.[4]

Disadvantages

1. High start-up cost.
2. No one size-fits all system.
3. Greater complexity.
4. Cannot be used for Intravenous route.
5. Infrastructure for exhaustible gas systems.
6. Higher requirement for training and maintenance. [4]

Raw Material

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. Outer shell material should be light weight and should have high strength for example polycarbonate. [5]

The Manufacturing Process: [6]

There are numerous methods of producing each needle-free injection system. The following process focuses on the production of an air-forced system. These systems are made through a step by step procedure which involves:

1. Molding the pieces,
2. Assembling and labeling the pieces ,and
3. Packaging

1. Molding the pieces

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

2. 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.

3. 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. [7]

Design of a Needle free Injection Device:

Nozzle:

The nozzle has two critical functions; it acts as the passage for the drug and as the surface which contacts the skin (fig.1). 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, 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 is shown in figure. 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.

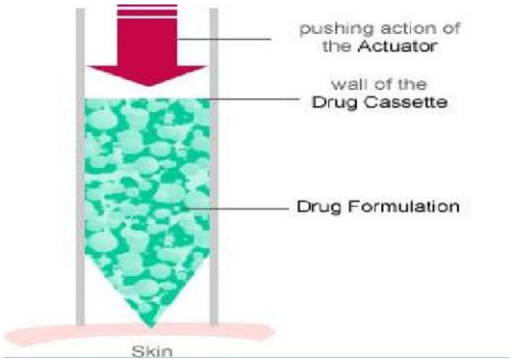
Pressure Source:

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 compressed gas in a vessel which is released at the time of injection.[7]

Fig 1: Components of Needle Free Injection Devices.

Working Mechanism Of Needle-Free Injection System:

Needle-free injection technology works by forcing liquid medication at high speed througha tiny orifice that is held against the skin. The diameter of the orifice is smaller than thediameter of a human hair. 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.3. From this figure, it is seen that the needle-less stream is much smaller than the average conventional injection needle.[8] This creates an ultrafinestream of high-pressure fluid that penetrates the skin without using a needle. The design must ensure that a sufficiently high pressure is generated to puncture the skin,while the subsequent pressure is reduced toensure that the molecule is deposited comfortably at a level that does not reach themuscle tissue. High-pressure delivery could potentially damage fragile molecules, such asmonoclonal antibodies. Successful delivery ofsuch molecules, therefore, requires a device with carefully controlled power nuances. Several companies are involved in developmentof this technology.[9]



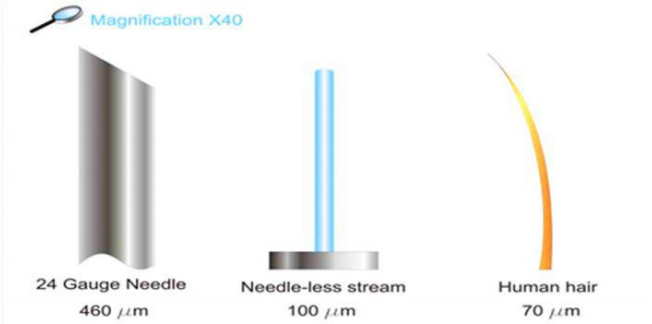


Fig 2: Mechanism of working. **Fig 3: Size comparison of a human hair, 24 gauge needle and drug stream.**

Types of needle free injection systems:[10]

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

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

Powder Injection:

Powder jet injectors deliver vaccines or drugs in dry powdered form into superficial layers of skin. The terms biolistic injectors and gene guns have also been commonly used for these injectors, with the latter term used exclusively for DNA delivery. 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 powders used in these systems require specific properties and specific size to ensure their stability and proper dispersion into the tissue. [10]

Principle:

Principle involved in powdered injection system is, the medications are delivered by pressurized contact of fluids with the skin. A known quantity of powder medication is put in a drug cassette which is opened by the compressed gas and thus the medication is delivered to tissue.

Mechanism:

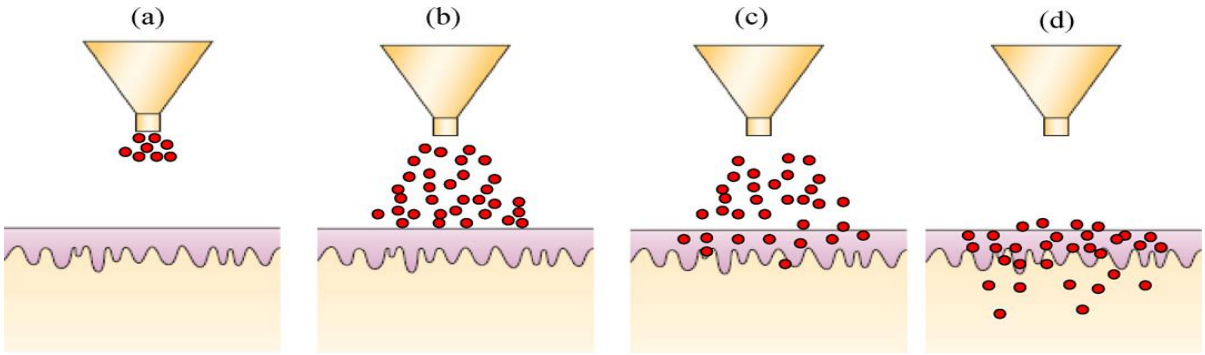


Fig. 4:. Schematic of drug delivery using powder injector (a) ejection of particles from nozzle, (b) impact of particles on skin surface, (c)penetration of particles across stratum corneum,(d) completion of delivery. Particles which penetrate into the skin are mostly distributed in stratum corneum and viable epidermis.

Basic design of solid jet injectors include compressed gas as the power source, a drug compartment containing particulate drug formulation, and a nozzle to direct the flow of particles. The drug compartment is closed with diaphragms on either sides, which are typically few microns thick. Upon triggering the actuation mechanism, compressed gas from a storage canister expands and pushes against the diaphragms, sequentially rupturing them. The flow of gas carries the drug particles with it. The particles then exit through a nozzle and impinge on skin & upon impacting on the skin; particles puncture micron- sized holes into stratum corneum by virtue of their momentum.(fig 4)[11]

Applications:[10]

1. Solid jet injectors have been studied for delivery of DNA encoding for viral and bacterial antigens using coated gold microparticles.
2. Induction of humoral and cell mediated immune response against influenza, hepatitis B and rabies has been shown in mice.
3. Protection against tumors has also been demonstrated by injecting DNA coated gold micro-particles and DNA encapsulated in polymeric particles.
4. An extensive review of preclinical DNA vaccination studies using solid jet injector systems in large animal models (swine and non human primates) has been published.
5. Clinical efficacy in humans has been demonstrated by induction of cell mediated and humoral immune response against hepatitis B using DNA coated gold micro-particles.
6. Phase I clinical studies for delivery of DNA vaccine against influenza showed humoral response.
7. Another human clinical study used cross-immunization regime with primary immunization using powder injector followed by intradermal injection as booster, and showed cell mediated response against malaria.

Advantages:

1. A small volume of material, shot through the skin as drug, is in powder form instead of liquid form, hence injection is painless.
2. The therapeutic agent will be more stable and there is no need of cold storage.
3. 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.
4. Protein drugs are very potent, and suitable for powder needle free injection systems.[12]

Disadvantage:

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.

Liquid Jet Injection:

Liquid jet injections employ a high-speed jet to puncture the skin and deliver drugs without the use of a needle. Since then, two main classes of liquid jet injectors have been developed. These are single-dose jet injectors, known as DCJIs (disposable cartridge jet injectors) and MUNJIs (multi-use-nozzle jet injectors) [10]. 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. [11]

Principle:

The basic principle of this injection is "if a high enough pressure can be generated by a fluid in intimate contact withthe skin, then the liquid will punch a hole into the skin and be delivered in to the tissues in and under the skin."[11]

Mechanism:

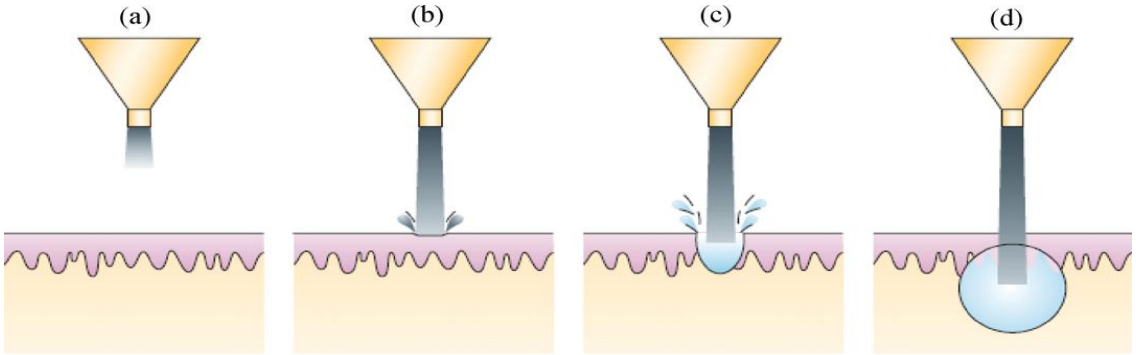


Fig. 5 .Schematic of drug delivery using liquid jet injector: (a) formation of liquid jet, (b) initiation of hole formation due to impact of jet on skin surface, (c) development of hole inside skin with progress of injection, (d) deposition of drug at the end of hole in a near spherical or hemispherical pattern (spherical pattern shown).

On triggering the actuator, the power source pushes the piston which impacts the drug-loaded compartment, which leads to a quick increase in pressure. This pushes the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200m/s. A schematic representation of injection process is shown in Fig. 5.The effect of the forceful stream of liquid 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 forceful stream of liquid increases the depth of the hole in the skin. The formation of a hole is believed to be due to a combination of skin erosion and fracture and is completed during the first few hundred microseconds. As the forcefulness of the liquid stream progresses deeper in the skin, velocity decreases until it does not have sufficient energy to continue whole formation. This completes the first phase of injection i.e. unidirectional skin puncture and followed by the second phase, multidirectional jet dispersion from the end point of penetration. 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.

Application:

MUNJIs have been used for mass immunization programs for diseases including measles, smallpox, cholera, hepatitis B, influenza and polio.

DCJIs have been used for delivery of several proteins. Most work has been done on delivery of insulin and growth hormones, while erythropoietin and interferon have also been delivered. [10]

Depot Injection:

Also known as projectile needle free injection technology. It is a very recent advancement of the technology. In this the drug is formulated into a slender, long, thin depot having enough robustness to transmit a driving force to a pointed tip, the tip is formed of a soluble inert material like sugar. The depot is driven into the skin with a sufficient force to penetrate the skin and fatty tissue. A typical depot is about 1mm in diameter which is adequate for most proteins and antibodies. The pressure of 3-8 mega pascals (MPa) is enough to puncture the skin with a sharp tipped punch. This is particularly useful and advantageous for drugs that are affective in the milligram dose range, and if, liquid forms of the drugs are unstable. [13]

Classification of Needle free drug delivery: [14]

Needle free drug delivery is classified into two types as follows:

1. Jet injector.
   - Spring load jet injector
   - Battery powdered jet injector
   - Gas powdered jet injector
2. Transdermal Patches.

Jet Injector:

Itaccelerate liquid droplets across the skin at high velocity and are used clinically to administer insulin, vaccines, and other drugs, but have had limited impact because of their size, cost and inability to reduce pain and injury.

There are three types of 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 drug. The activated spring load must be redrawn manually for the next administration. Examples: Dermojet®, Medi-jector® [4]

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.

Examples: Intra Dermal Application of Liquids (IDAL) ®- Intervet, Boxmeer. [4]

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.

Examples: Biojector®, Pulse®, Needle-Free Felton, Lenexa, Ks. Agro-Jet®/Med-Jet®- Mit, Montreal, Quebec,Canada.[4]

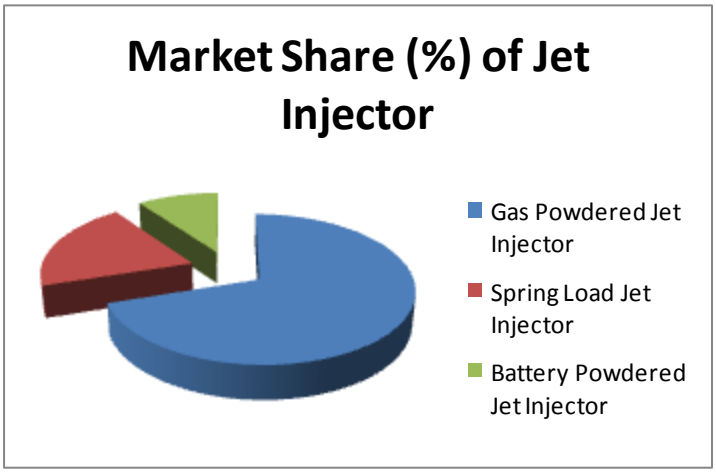


Fig.6: Market Share (%) of Jet Injector.

Transdermal Patches :[14]

A transdermal patch, which may also be considered a Transdermal Drug Delivery System (TDDS), is defined as a flexible, multi-layered, pharmaceutical single dose preparation of varying size containing one or more active substances to be applied to the intact skin for systemic absorption. This is normally formulated with pressure-sensitive adhesives that assure the adhesion of the preparation to the skin. A transdermal patch includes a baking sheet, impermeable to the active substance and normally impermeable to water. The releasing surface of the patch is covered by a protective liner to be removed before applying the patch to the skin.

Types of Transdermal Patches:[15]

Single-layer Drug-in-Adhesive:

The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive:

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing. (Fig 7)

Reservoir:

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system t rate of release is zero order 8. (Fig 8)

Matrix:

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. Also known as a monolithic device. (Fig 9)

Vapour patches:

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapor. The vapor patches are new on the market and they release essential oils for up to 6 hours. The vapor patches release essential oils and is used in cases of decongestion mainly. Other vapor patches on the market are controller vapor patches that improve the quality of sleep. Vapor patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market 12.

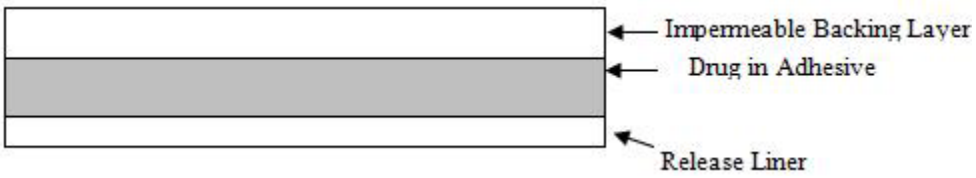


Fig. 7: Design of drug in adhesive type transdermal patch.

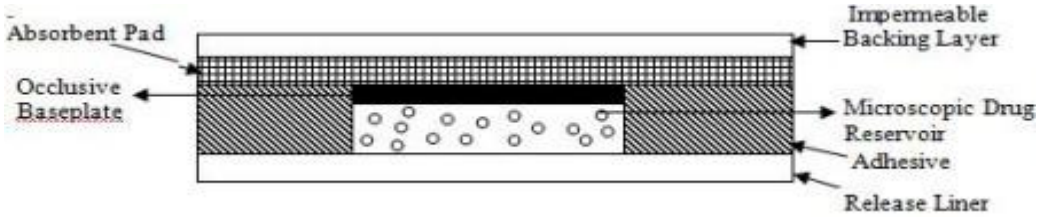


Fig. 8: Design of reservoir type transdermal patch.

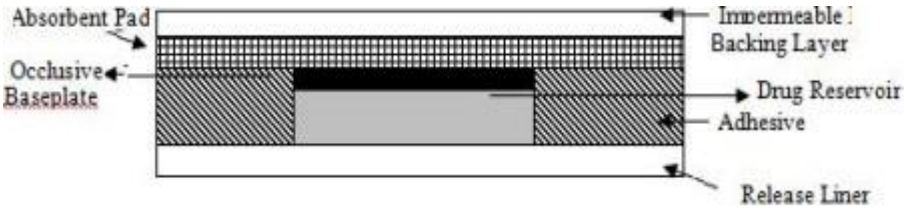


Fig. 9: Design of matrix type transdermal patch.

Different Technologies of Needle Free Injection:

Mhi 500:

It is a spring loaded device use for injecting insulin without the use of needle. This device forces the fine liquid stream of insulin at high speed which penetrates across the skin. The suitable site for injection is abdominal wall, buttocks, and upper thighs. This technology achieved the Food and Drug Administration (FDA) approval in 1996 for the subcutaneous delivery of insulin. [16].

Fig.10 :Mhi Jet 500.

Recojet:

The Mumbai-based Shreya Life Sciences Pvt Ltd has launched recombinant human insulin under the brand name Recosulin and a needle-free insulin delivery device - Recojet.[17].

Fig.11: Recojet.

Serojet:

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. [18].

Fig. 12:Serojet.

Iject:

The Iject is a small, lightweight, gas-powered injection system being developed 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 accepts pre-filled medication cartridge The Iject is a versatile injection system that can be adapted to deliver subcutaneous, intramuscular, and intradermal injections, as well as a variety of injection volumes. By integrating key design elements from Bioject's other systems, the Iject uses proven needle-free technology.[19]

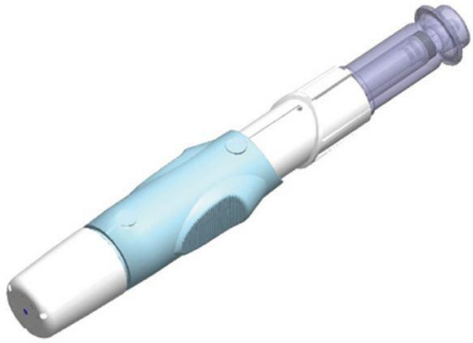


Fig.13: Iject.

Vitajet 3:

The Vitajet 3 is an easy-to-use, economical needle-free injection system for delivering insulin. With disposable nozzles that are replaced once-a-week, the Vitajet 3 offers the quality of a reusable medical product, with the convenience and safety of a sterile disposable. The Vitajet 3 received the FDA marketing clearance for delivering subcutaneous injections of insulin in 1996. Since then, the system has been used to deliver hundreds of thousands of injections, safely, economically and without the use of a needle.[18]

Biojector 2000:

The Biojector is a needle free injection system that has been used to deliver millions of injecton without any complication. It is use to deliver drug intramuscularly, subcutaneously and intradermaly upto 1 ml in volume. [19]

Fig. 14: V itajet3

Fig.15: Biojector 2000.

Cool Click:

Bioject developed the cool.click needle-free injection system for delivering Saizen recombinant human growth hormone. In some children, naturally occurring growth hormone is absent or is produced in inadequate amounts. In these cases, Saizen or growth hormone replacement must be injected to maintain normal growth . Cool.click is a customised version of Bioject‟sVitajet 3 needle-free injection system. The system includes customized dosage features to accurately deliver variable doses of Saizen and was designed with bright colors to make the injector attractive and non-threatening to children. The cool.click received FDA market clearance for delivering subcutaneous injections of Saizen in June, 2000.[18]

Fig. 16: Cool Click.

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 . No other single-use needle-free delivery technology provides the same level of performance as the Mini-Ject technology with the ability to target specific tissue layers over such a broad range of drug volumes (0.1 mL to 1.3 mL) and viscosities.[4,20]

Fig .17:Biovalve Mini-jectTecnology.

Antares' Medi-Jector Vision technology:

Medi-Jector Vision technology which is used to deliver insulin is developed by Antares Pharma. It is the latest, Reusable, variable dose, spring powered device for insulin delivery. Human growth hormone can also be delivered by this technology. Due to its plastic, disposable needle free syringe the patient can see and monitor the dose prior to injection. (Fig 18)[20]

Implaject:

Simple, hand held needle free injection device. It can be configured to be reusable with disposable cartridges.(Fig 19)[20]

Fig .18: Antares' Medi-Ject Vision Technology.

Fig.19: Implaject.

Crossject:
Prefilled, single use disposable NFI. It uses chemical reaction to generate propellant at the time of administration.[20]

Fig.20: Crossject.

Powderject:
Painless delivery of DNA vaccines to the skin in a dry formulation can be achieved by this technology.[20]

Fig.21: Powderject.

Injex 30:

Spring powered hand held device with disposable ampoules that delivers 0.05-0.3 ml. Focused on insulin delivery. [20]

Fig.22: Injex 30.

CONCLUSION

Due to the pain-less nature of this system, it has got the potential to replace all current needle systems to make parenteral route more patients compliant. Needle-less technology has the best alternative to deliver the medicament in to the skin without having a pain. Other benefits include very fast injection compared with conventional needles and no needle disposal issues. Many of these needle-free alternative technologies are in the development stage. Companies are still working on producing devices that are safer and easier to use.

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REFERENCE

1. Kumar Rapalu Bharath, "Needle Free Injection System," The Pharma Innovation 1.9 (2012): 52-72.
2. Balagani Pavan Kumar and M. Sindhuri, "Needle Free Drug Delivery System: An Update Of Upcoming Evolution," 4.2 (2015): 409-432.
3. Kadam Vaishali, et al, "A Review On Needle-free Injection System," World Journal of Pharmacy and and Pharmaceutical Science 3.3 (2014): 763-780.
4. Kale Tejaswi R., Munira Momin, "Needle Free Injection Technology- An Overview," Innovations in Pharmacy 5.1(2014): 1-8.
5. Khan Mohd Tosif, et al, "The Needle Free Injection Technology," (2015).
6. P. Raghuveer, et al, "A Review on Needle Free Drug Delivery System," World Journal of Pharmacy and Pharmaceutical Science 5.6(2016): 449-465.
7. Patwekar S. L., et al, "Needle free Injection System," Int. J of Pharmacy and Pharmaceutical Science 5.4 (2013): 14-19.
8. R. Hirlekar and P. Jose, "Needleless Injection System," Int. J of Pharmaceutical and Chemical Sciences 2.4 (2013): 1857-1863.
9. Sanghi D. K. and Rakesh Tiwle, "An Update: On Needle Free Injections," Int. J of Pharmaceutical, Chemical and Biological Sciences 4.1(2014): 129-138.
10. Arora Anubhav, et al, "Micro Scale Devices for Transdermal Drug Delivery," Internation Journal of Pharmaceutics, 364.2 (2008): 227-235.
11. Kohle S. and S. Sontake, "A Review on Needle free Drug Delivery System," Int. J of Current Pharmaceutical Research, 5.2 (2013): 15-20.
12. C. K. Sahoo, et al, "A New Sight in Needle Free Injections," Int. J of Universal Pharmacy and Bio Sciences 6.1 (2017): 97-109.

13. Verma Mayak, Khan Shahid, et al, "Needle Free Drug Delivery System: A Review," World Journal of Pharmacy and Pharmaceutical Science 5.4 (2016): 817-832.
14. Harvinder S. Gill and Mark R. Prausnitz, "Does Needle Size Matter?," Journal of Diabetes Seience and Technology, 1.5(2007): 725-729.
15. Dhiman S. et al, "Transdermal Patches: A Recent Apporch to New Drug Delivery System," Int. J of Pharmacy and Pharmaceutical Science, 3.5 (2011): 26-34.
16. www.diabetesuffolk.com
17. www.thehindubusinessline.com/blinr/2004/12/13/storiec/2004121302130300.html
18. Vishnu P, Sandhya M., et al, "Needle free Injection Technology: A Review," International Journal of Pharmacy, 2.1(2012) 148-155.
19. www.bioject.com
20. www.uniassignment.com/.../the-needle-free-injection-technology-biology-essay.

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