Review Article

Needle Less Injectable Systems: A Review

K. Lalitha, V. Vasu Naik*, K. Lakshmi and GRB. Tripura

Department of Pharmaceutics, Hindu College of Pharmacy,
Guntur - 522 002, Andhra Pradesh, India.

ABSTRACT

Needle less injection systems are novel ways to introduce various medicines into patients without piercing a conventional needle. Needle less injection technology was developed to reduce the number of needle stick accidents and associated problems. This review describes needle less injectable systems involving the generation of force by using compressed gas upon actuation in order to deliver a drug at very high speed through a nozzle. Some of technologies are Biojector 2000,Cool click, Serojet, Jupiter Jet, Antares medi-Jector Vision technology etc. Organizations such as WHO and CDC (Centre for Disease Control) and groups like Gates Foundation have supported the development of needle-free alternatives for drug delivery. This technology is used to deliver not only drugs but also proteins, peptides, monoclonal antibodies, small molecules and vaccines. Now a days, This become more safer method and increases patient compliance.

Keywords: Needle less injection systems, Technology.

INTRODUCTION

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 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.

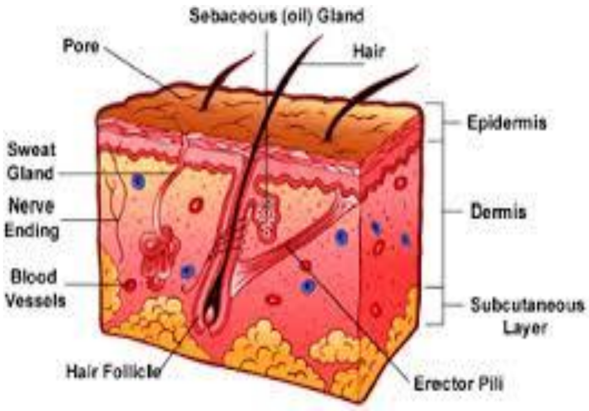
STRUCTURE OF HUMAN SKIN

Human skin is generally made of two layers i.e, the epidermis and dermis.

Epidermis

It is the external layer of the skin which is mainly composed of various layers of keratinocytes, melanocytes, Langerhans cells and Merkel cells. It acts as a physical and chemical barrier between the body and external environment. The epidermis is stratified squamous epithelium in nature. It has four layers:

1. Stratum basale
2. Stratum spinosum
3. Stratum granulosum
4. Stratum corneum



Dermis

It is the area of supportive tissue between the epidermis and subcutis. The dermis mainly consists of sweat glands, hair roots, nerve cells, and fibers, blood and lymph vessels. It is mainly composed of a thin papillary and reticular layer. Its main function is to protect the body from stress and strain. A sense of touch and heat is provided by the mechanoreceptors harboured by the dermis.

Hypodermis

It is the layer of loose connective tissue and fat that lies beneath the dermis. Its role is put together the skin and underlying bone and muscle and supply it with vessels and nerves.

COMPONENTS OF NEEDLE FREE INJECTION DEVICE

Needle free injection device consists of 3 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 0.127 mm, comparable to a25-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.

Component3-Pressure source

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. 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 influenced 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 mono clonal antibodies. Hence, devices may vary in design depending upon the drug for which they are used.

Types of Needle Free Injection Systems

Needle free technologies are of 3 types

a) Powder injections
b) Liquid injections
c) Depot or projectile injection.

a) Liquid based NFI

These technologies are used by the same basic principle to deliver the drug, if a high enough pressure can be generated by a fluid in intimate contact 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. The device has sufficient pressure to the skin.

b) Powder injections

For the purpose of delivery via skin, the particles must only pierce the outermost barrier of the skin i.e. the stratum corneum. So, drugs delivered reach the circulatory system at a faster rate as compared to those administered by subcutaneous injection. The most common orifice size is 0.127mm,compared to a 25 guage needle, which is about 1mm.So, process is completely painless.

The powder ject systems are powdered by a manufactured helium gas aluminium micro cylinder of ampoule design and use a drug cassette or package to introduce the powder into the gas flow. In operation, when the device is pressed against the tissue site to be treated at that time the cassette for delivery of its payload to the tissue. The gas does not actually penetrate the skin, instead, through a silencer it is reflected back in to the device. The powder used in these systems requires specific size to ensure their stability and proper dispersion into the tissue.

c) Depot or projectile NFI

Depot injections are given in the muscle where they create a store of a drug which is released continuously over a specified period of time.

THE MANUFACTURING PROCESS

1. **Making the pieces**

In the first step from plastic pellets the component plastic pieces produced. This is done by a process called injection molding. Pellets of plastic are put into a large holding bin on an injection molding machine. To make them flowable plastic pellets are heated. After this the material is passed through a hydraulically controlled screw. As the screw rotates, the plastic is directed through a nozzle which then injects into a mold. The mold is made up of two metal halves that from the shape of the part when brought together. When the plastic is in the mold, for a specified amount of time it is held under pressure and then allowed to cool. After cooling, the plastic inside hardens. The mold pieces are separated and the plastic part falls out onto a conveyor. The mold then closes again and the entire process is repeated. After the plastic parts are ejected from mold, the manual inspection are carried out to ensure that there is no significantly damaged parts are used during the process.

2. Assembling and labelling

The parts are next transported to an assembly line. Pieces are inserted into an main housing and buttons are attached. Machines apply markings that show dose levels and force measurements. These machines are specially calibrated so each printing is made precisely. Depending on the complexity of the device, human workers or machines may assemble devices. This involves inserting the various pieces into the main housing and attaching any buttons.

3.Packaging

After the assembly step, the injection devices are first wrapped in sterile films and then put into cardboard or plastic boxes. Each part is packaged so, movement is minima which prevent damage. For consumer products, an instruction manual is provided which includes the safety information. These boxes are then stacked on pallets and shipped via truck to distributors.

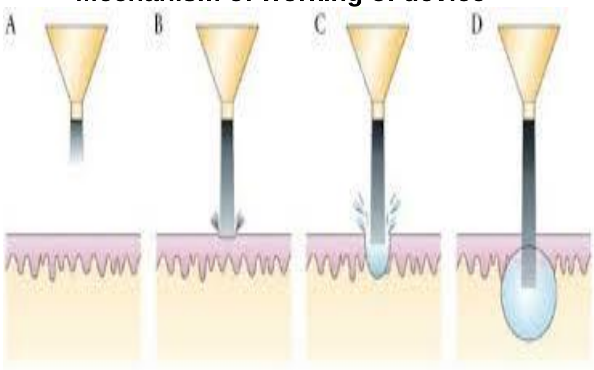
QUALITY CONTROL

Through the manufacturing process, Quality control checks are done. Line inspectors ensure that the plastic components match with the previously determined specifications. The first test method is Visual inspections, but to check the dimensions (size and thickness) the measuring equipment is also used. Instruments like laser micrometers, callipers and microscopes are used. Inspectors also check to make sure the printing and labelling is correct and that all parts are included in the final packages. Since these devices can have various safety issues, their production is strictly controlled by the Food and Drug Administration(FDA). Each manufacturer must conform to various production standards and specifications. Detailed records related to ensure that these companies are following good manufacturing practices.

MECHANISM OF WORKING

Needle-free injection technology works by forcing liquid medication at high speed through a tiny orifice that is held against the skin. The diameter of the orifice is smaller than the diameter of a human hair. This creates an ultrafine stream of high-pressure fluid that penetrates the skin without using a needle. When administered through the skin, an ultrafine stream of fluid penetrates the skin, delivering the vaccine in a fraction of second to the skin, subcutaneous tissue, and intramuscular tissue. Injection event requires less than 0.5 seconds.

Mechanism of working of device



Transdermal injections (visualizing the process)

VARIOUS THECHNOLOGIES

1) Bioject's needle free injection technology

Bioject was found in 1985 to improve the comfort and safety of routine injections. An ultra-fine stream of high-pressure fluid is created. Without using a needle fluid penetrates the skin. Bioject has developed a broad technology platform for delivering many different types of medications and vaccines to the subcutaneous and intramuscular depths.

1) Biojector 2000

Biojector 2000 is a durable, professional grade injection system designed for healthcare providers. The Biojector 2000 is the only needle free system in the world cleared by the

FDA to deliver intramuscular injections. The system can also deliver subcutaneous injections, and is being used for intradermal injections in clinical trials. More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. In high-risk situations, such as delivering injections to patients known to be infected with HIV or hepatitis, the Biojector, is an ideal injection system.

2) 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, Siazen or growth harmone replacement must be injected to maintain normal growth. Cool click is a customised version of Bioject's Vitajet 3 needle-free injection system. The cool click received FDA market clearance for delivering subcutaneous injections of siazen in June, 2000.

Figure 6

3) Serojet
Serojet is a customised version of Bioject's Vitajet needle freer injection system. The serojet is a needle-free injection free system for delivering Serostim recombinant growth hormone for treatment of HIV associated wasting in adults. The Serojet received FDA market clearance for delivering subcutaneous injections of Serostim in March 2001.

4) Vitajet 3
The device consists of disposable nozzle which are replaceable in week. 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. This device is used for delivery of insulin subcutaneously. It received FDA approval for marketing in 1996. Vitajet3 has developed a broad technology platform for delivering many different types of medications and insulin to the subcutaneous and intramuscular depths.

5) The Zeta Jet ™
Bioject®Zeta Jet ™
The Bioject®ZetaJet ™ ,Bioject's latest advance in advance in needle- free delivery systems, consists of two components, the portable injector and an auto- disabling disposable syringe. It is intented to deliver vaccines and injectable medications either subcutaneously or intramuscularly and is indicated for both professional use and home use for patients who self-inject. The syringe assembly has a unique "auto-disable" feature that prevents re-use of the syringe. The Bioject ®ZetaJet™ has FDa clearance for delivering subcutaneous or intramuscular injections of liquid medication, including vaccines and other injected medications. It has ability to deliver to all three injection depths: Intramuscular, subcutaneous or intradermal injection volumes range from 0.05 mL to 0.5 mL.

6) Jupiter jet
The jupiter jet, a unique hand-held device that is capable of administering small volumes (0.03 to 0.2 mL) of drugs at SC, IM or ID depths. The Jupiter Jet is very easy to use – essential traits for a product targeting the self-injection market or procedures with repeat injections.

7) Mhi-500

Compared with a needle injection system, the mhi-500's needle-free insulin delivery technology improves the dispersion of the insulin throughout the tissue. This jet then penetrates the tissue, depositing the insulin in the subcutaneous layer. The jet is created by forcing the insulin through a precisely designed nozzle that is held in contact with the tissue during the injection. The system was approved by FDA in 1996 and for sale throughout Europe.

Summary of marketed products

Product name	Company	Type of system	Actuation mechanisn	Depth of penetration	Drug volume	Comments
Biojector 2000	Bioject	Liquid based NFI	Compressed gas	Subcutaneous, Intramuscular	1	Used to deliver vaccines
Vitajet3	Biojector	Liquid based NFI	Spring	Subcutaneous	0.02-0.5	Can be self administered
Intraject	Weston medical	Liquid based NFI	Compressed gas	Subcutaneous	0.5	Delivered drug in less than 60 milli sec.
Penjet	Penjet corporation	Liquid based NFI	Compressed gas	Intramuscular, Subcutaneous, Intramuscular	0.1-0.5	Low cost, esay to operate
Vision intraject	Aradigm	Liquid based NFI	Compressed gas	Subcutaneous	0.5	Deliver drug in less than 60 milli sec.
Cross jet	Cross jet	Liquid based NFI	Spring	Intramuscular, Subcutaneous, Intramuscular	0.2-1	Operating is based on novel gas tech.
Miniject	Biovalve	Liquid based NFI	Spring	Intramuscular, Subcutaneous,In tramuscular	0.1-0.3	Candeliver wide range of drugs.

APPLICATIONS

1. Intraject (Weston medical) technology used to deliver drugs including proteins, peptides, monoclonal antibodies, small molecules and vaccines.
2. Medi-Jector vision (Antares pharma, Inc.) technology used to create a micro thin stream of insulin that penetrates the skin.
3. Powderject 17 (powder ject pharmaceuticals) technology delivered inulin to hairless guinea pigs, delivary of large macro molecules across the skin, used for intradermal.
4. DNA immunization against influenza virus in mice.
5. Jet injectors technologies deliver proteins such as B-interferon as well as small organic conventional therapeutic agent such as lidocaine (lignocaine)for local anaesthesia.
6. Insulin therapy
   a. The mhi -500 needle-free device is used

It uses a spring, which is housed within the body of the device. A simple twisting motion winds up the spring and a button is pressed to discharge the energy generated by the recoil of the spring.

ADVANTAGES OF NEEDLE FREE INJECTION TECHNOLOGY

1. Eliminates needle phobia
2. Increases patient compliance and vaccination rate
3. Elimination of broken needles.
4. Consistent vaccine delivery
5. Reduced vaccine volume
6. Higher dispersion pattern
7. Easy to transport and store without refrigeration
8. Excellent dose response is observed with increased drug doses.
9. Fewer injection site lesions
10. Lower pain and stress

DISADVANTAGES
1. Higher start-up costs
2. Trained personnel
3. Lack of worker confidence
4. Infrastructure for exhaustible gas systems.

CONCLUSION
Needle free technology offers the very apparent benefit of minimizing patients fear regarding the use of needle. Other benefits comprise very fast injection as compared to traditional needles and needle disposal issues are rarely seen.
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, bio technology 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 important role in the novel drug delivery technologies market in the coming years.

REFERENCES

1. Gopalan J, Divya G and Chakravorty D. Needleless Vaccine Delivery Using MicroShock Waves. Clinical and Vaccine Immunology: CVI, journal of American Society for Microbiology. 2011;18(4):539–545.
2. Reddy MS, Kumar M, Kumar KS, Goli A and Kumar PS. Review on Needle free drug delivery systems. International Journal of Review in Life Sciences. 2011;1(2):76-82.
3. Khalilullah Sd, Manasa K, Satish babu S, Dileep CH, Suresh P, Brahmaiah B, Nama Sreekanth and Patan Adamkhan. A Review on Needle Free Injection.
4. Madan Mohan Gupta, Vinesh Kumar and Pawan Kumar Basniwal. Needle Free Injection: An Alternate Approach of Injection, The pharma review (February - March, 2008). Available from: URL: http://www.kppub.com/articles/needle-freeinjection-015/needle-free-injection.html
5. Bhagya Sri, Abha Doshi,Yashwanth Malode and Balu Misal. Review on needle free technology. International journal of Pharma research. 2013;2(9):30-36.
6. Needle free insulin drug delivery by Preeti Patni, Dhanila Varghese, Neelam Balekar and Jain DK. Indian journal of Pharmaceutical sciences. 2006;68(1):7-12.
7. Painless and needle free supersonic injection technologies, by Dr. J K Patel, pharmainfo.net, 10/04/2006.
8. Going from needles to needle free injectable, drug development and delivery, February 2005; 5 (2), Posted On: 3/28/2008.
9. Kim YC, Jarrahian C, Zehrung D and Mitragotri S. M. R. Delivery systems for intradermal vaccinations by Prints, Current topics in microbiology and immunology. 2012;351:77-112.
10. Available from: URL: http://pharmagate.net/injex/what-is-injex-30/, accessed on 15th January 2014.
11. Available from: URL: http://www.injex.com/zahnmedizin, accessed on 15th January 2014.