

## A review on needle free injections

### ABSTRACT

At present scenario many researchers are working to develop technology that promises to deliver the drug in more efficient and less painful way in order to produce the therapeutic effects. Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. Needle free injection gives very effective injections for a wide range of drugs. Needle free systems are designed to avoid the problems associated with conventional needles making them safer, less expensive, and more suitable. Additional benefits include very fast injection compared with conventional needles and no needle disposal issues. This review intends to throw light on the basic mechanisms by which this technology works, different types of technologies available at present and its applications.

**Keywords-** Needle free injection, drug delivery, needleless technologies.

### INTRODUCTION:

At present scenario, many researchers are working to develop technology that promises to make the administration of medicine more efficient and less painful<sup>1</sup>. There are a variety of problems associated with the hypodermic needles used in injections. These include relatively high cost of the needles, lack of reusability i.e. needle syringe should be sterilized, additionally; many people have a fear of needles or needle-phobia, which causes them to avoid treatment<sup>2</sup>. These drawbacks have led to the development of alternative delivery systems to needle injections. Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. In general, 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<sup>3</sup>.

These systems are novel ways to administer various medicines into patients systemic circulation without piercing the skin with a conventional needle. Needle-free injection is a fast, effective route of administration<sup>4</sup>. These technologies have been developed for injecting liquid formulations, as well as injecting drugs and vaccines in a solid dosage form.

In 1853, first hypodermic syringes were first developed by French surgeon, Charles Gabriel Pravaz, however there are minor changes in technology since last few decades<sup>5</sup>.

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 pierce the skin and deposit the drug in underlying tissue<sup>6</sup>. These devices were used extensively to inoculate against infectious diseases and were later applied more generally in large scale vaccination program<sup>7</sup>.

### ADVANTAGES<sup>8, 9, 10, 11, 12</sup>

1. No under- or overdosing condition of the drugs.
2. Useful in case of patients with needle phobia.
3. It delivers pain-free injection. Prevents skin puncture hazards and its destruction; also does not cause problem of bleeding or bruising and minimal skin response.
4. Improved patient compliance especially in chronic administration of drugs.
5. No need to visit hospitals / experts for injections, i.e., self-administration is feasible.
6. No specific disposal requirements.
7. No risk of cross contamination from needle-stick injury.
8. Amount of medicine delivered and the depth can be adjusted.

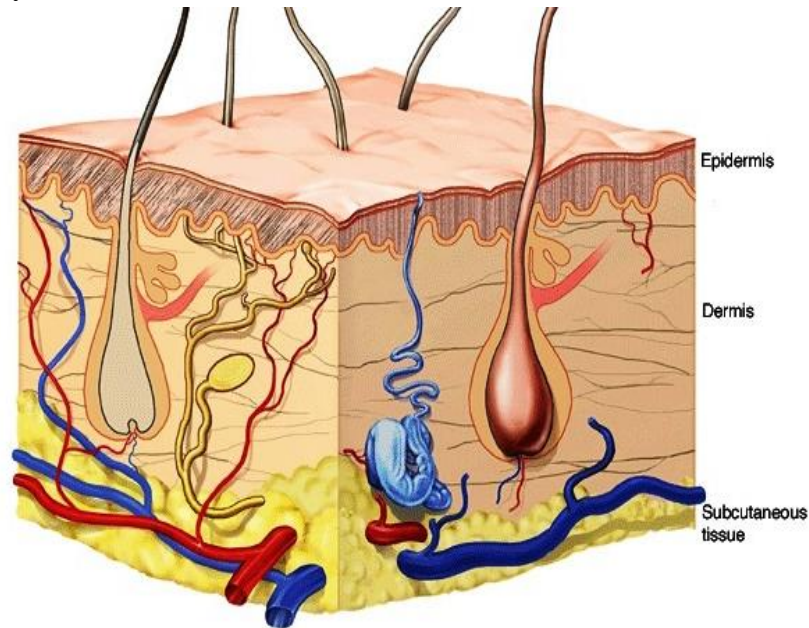
9. Vaccines can be delivered in powdered forms as well as viscous liquids.
10. Better drug stability during storage as it is delivered in dry powder form.

**Disadvantages of needle-free injection<sup>13,14</sup>**

1. Method is complex and expensive.
2. All systems are not fitted into one size.
3. Need for personnel training and maintenance.
4. It is not applicable for Intravenous route.?

**Structure of skin**

The skin is one of the largest organs in the body in surface area and weight. The skin consists of two layers: the epidermis and the dermis. Beneath the dermis lies the hypodermis or subcutaneous fatty tissue.



**Figure 1: Structure of skin**

**Epidermis:**

The epidermis, the outermost layer of skin, provides a waterproof barrier and creates our skin tone. It forms the waterproof, protective wrap over the body's surface and is made up of stratified squamous epithelium with an underlying basal lamina. There are no blood vessels in epidermis, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis<sup>15</sup>.

**Dermis:** The dermis, beneath the epidermis, contains tough connective tissue, hair follicles, and sweat glands. The dermis is tightly connected to the epidermis by a basement membrane. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the stratum basale of the epidermis<sup>16</sup>.

**Hypodermis:**

The hypodermis is not part of the skin, the deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue and elastin<sup>17</sup>.

**COMPONENTS OF A NEEDLE FREE INJECTION DEVICE**

Devices may vary in design depending upon the drug for which they are used.

**1. Injection device**

It consists of a drug chamber and made up of plastic. Sterility is maintained throughout the device<sup>18</sup>.

## 2. Nozzle

The nozzle serves as passage for the drug. It has an orifice through which the drug enters skin after injection. The diameter of orifice typically is 100  $\mu\text{m}$ . The nozzle fires drug particles at a typical speed of 100 m/s with a depth of 2 mm. Thus this injection is painless; the patient feels tap of gas on the skin which is like flicking finger against the skin<sup>19</sup>.

## 3. Pressure source:

The pressure source can be a mechanical method, stores energy in a spring and is released by pushing a plunger to provide the necessary pressure. It is important for delivering a drug forcefully into the systemic circulation via the skin. The most popular gases used in devices are carbon dioxide or nitrogen<sup>20</sup>.

## MECHANISM

The mechanism generates force by using compressed gas (such as carbon dioxide or nitrogen) to propel the drug through an orifice at a very high speed. While administration of drug occurs through the device, an ultra-fine stream of fluid penetrates through the skin layers which deliver the drug very quickly into the systemic circulation<sup>21</sup>. The total time required to deliver an injection is less than 1/3 of a second and occurs in three stages:

**Stage 1-** the peak pressure phase, optimal pressure used to penetrate the skin (< 0.025 sec).

**Stage 2-** the delivery or dispersion phase (~ 0.2 sec).

**Stage 3-** the drop-off phase (< 0.05 sec).

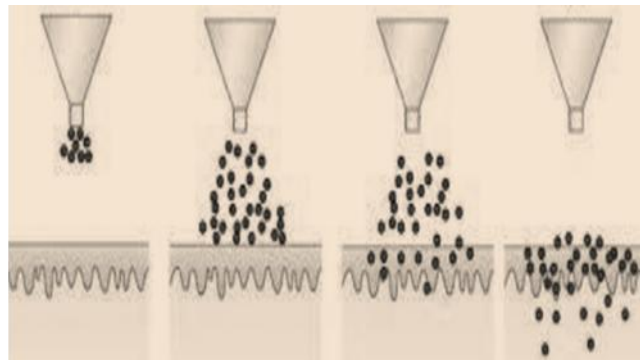
This pressure profile is consistent with each administration of vaccine ensuring each animal is vaccinated at the proper tissue depth. The needle-free injection technology improves the dispersion of medication throughout the tissue<sup>22</sup>. As the fluid stream forces its way through the tissue, it follows the path of least resistance, resulting in a widely dispersed, spider-web-like distribution of the medication<sup>23</sup>.

## TYPES OF NEEDLE FREE INJECTION SYSTEMS

### 1. Powder injections

These consist of a solid drug content filled in chamber and a nozzle for firing drug particles into the skin by utilizing compressed gas as the power source. A small volume of material, shot through the skin as drug, is in powder form instead of liquid form, hence injection is painless. The injection has a few microns thick diaphragm on either side of the chamber to cover the drug chamber.

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. Protein drugs are very potent, and suitable for powder needle free injection systems<sup>24</sup>.



## Figure 2: Mechanism of a powder injection

### 2. Liquid injections

The basic principle of this injection is generation of high enough pressure by a fluid in intimate contact with the skin, to deliver liquid by punching a hole into the skin. These systems use gas or spring, pistons, drug loaded compartments and nozzles having orifice size of about 150 to 300  $\mu\text{m}$ <sup>25</sup>.

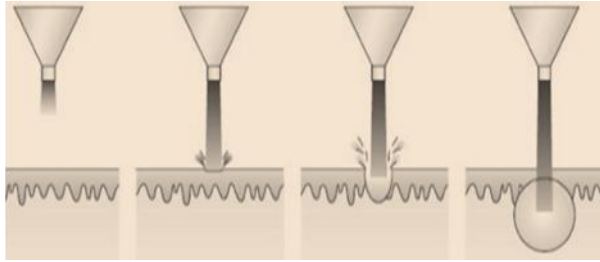


Figure 3: Mechanism of a liquid injection

### 3. Depot or projectile injections

These 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<sup>26</sup>.

### Types of injections

The needleless injections are mainly categorized into three types on the basis of the power source used in it.

(1) **Spring loaded injector**- The spring loaded injector uses a spring mechanism which is drawn back to push the drug into the underlying tissue where the drug dissolves and is released into the blood stream. The activated spring load must be redrawn manually for the next administration. Examples include Dermojet®, Medi-jector®<sup>27</sup>.

(2) **Battery powered injector**—Use of electricity as source of energy. It consists of a small rechargeable battery pack to retract the dosing device. The dosing device has an electric piston which is automatically redrawn after dosing. It is used for subcutaneous, intramuscular or transdermal delivery of drug. Examples include intradermal application of liquids (IDAL) ®- Intervet, Boxmeer<sup>28</sup>.

(3) **Gas powered injector**- It is typically made of three components. 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 include Needle-Free-Felton, Biojector®, Pulse®, Lenexa, Ks. Agro-Jet®/Med-Jet®- Mit<sup>29</sup>.

## RECENT NEEDLE-FREE INJECTION TECHNOLOGIES

### 1. Serojet

The device is designed for delivering Serostim recombinant human growth hormone administered subcutaneously. The Serojet device is tailored from Vitajet technology. This is used for treatment of HIV associated wasting in adults and was approved by FDA in March 2001 for marketing<sup>30</sup>.

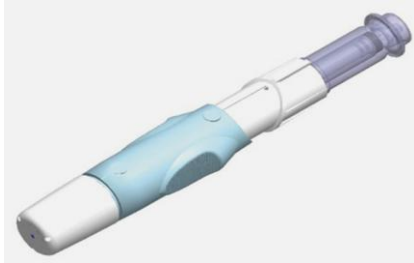


**Figure 4: Serojet**

## 2. Iject

It is a product of the Bioject Company as a second generation gas powdered injection system. The Iject is a pre-filled single-use disposable injection device configured to administer 0.5 to 1.00 ml subcutaneous or intramuscular injections.

The device is initiated by rotating the trigger sleeve 180 degrees. By advancing the trigger sleeve, the injection is administered, where the nozzle is placed against the injection site<sup>31</sup>.



**Figure 5: Iject**

## 3. Injex

Injex system offers administration of local anesthesia. It consists of an injection ampoule having orifice of 0.18 mm. From this orifice, the drug is fired under dosed pressure into the submucosa. 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<sup>32</sup>.



**Figure 6: Injex**

## 4. Bioject®Zetajet

It consists of two components, the portable injector and an auto disabling disposable syringe. It is intended 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<sup>33</sup>.



**Figure 7: BioJect**

## 6. Cool click:

Bioject developed it 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<sup>34</sup>.



**Figure 8: Cool click**

## 7. Vitajet

It received FDA approval for marketing in 1996. It consists of disposable nozzles which are replaceable once in week and used for delivery of insulin subcutaneously<sup>35</sup>.



**Figure 9: Vitajet**

## 8. Mhi-500

This device is used for subcutaneous administration of insulin. The system was approved by FDA in 1996 and for sale throughout Europe. The device creates a fine jet of insulin through the nozzle penetrating skin tissues of the subcutaneous layer<sup>36</sup>.

## 9. Madajet

It is commonly used in dentistry. It works by using pneumatic pressure to discharge local anesthetic. This stream makes a wheel of about 5 to 6 mm in diameter at the base of injection. The device injects a volume of 0.1 cc per injection intradermally<sup>37</sup>.

## 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<sup>38</sup>.
2. Lidocaine hydrochloride, a local anesthetic is suitable to be delivered needle free.
3. Heparin (an anticoagulant), erythropoietin, lidocaine hydrochloride (a local anesthetic) and various vaccines can be administered through needleless injection<sup>39</sup>.

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

## CONCLUSION

In the developing world, there are major challenges of disease transmission through re-use of needles. There appears to be tremendous opportunity for needle-free technology in pharmaceutical industry. Needle Free Injectors are easier to use, more efficient, more reliable,

much safer and have no disposal problems. Additional benefits include veryfast injection as compared with conventional needles.

Acceptance by patients, continuing developments and lowering costs all make needle free systems the best method for vaccinations. Not only it can benefit in increasing product sales, it has the added potential to increase compliance with dosage regimens and improved results.

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.

There is a need to train and educate the workers about this technology. Start-up and training costs may also affect the interest in this technology for some producers. 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.

## REFERENCES

1. Sanghi DK, Tiwle R, An update: on needle free injections, *International Journal of Pharmaceutical, Chem and Biolog Sci.* 2014; 4(1): 129-138.
2. Houser TA, Sebranek JG, Bass TJ, Thacker BJ, Nilubol D, Thacker EL. Feasibility of transdermal, needleless injections for prevention of pork carcass defects. *Meat Science.* 2004; 68(2); 329-332.
3. Kolhe S, Sneha S. A review on needle free drug delivery system, *Int J Curr Pharm Res.* 2013; 5( 2): 15-20.
4. Kale TR, Momin M. Needle free injection technology - An overview, *Inn in pharm.* 2014; 5(1):1-8.
5. Jones GF, Rapp-Gabrielson V, Wilke R, Thacker EL, Intradermal vaccination for *Mycoplasma hyopneumoniae*. *J. Swine Health Prod.* 2005; 13:19-27.
6. Hirlekar R, Jose P. Needleless Injection System, *Int J of Pharm and Chem Sci.* 2013; 2 (4):1857-1863.
7. Shivanand P, Patel J, Patel K. Various emerging technologies in insulin delivery system. *Int J of Pharma Research and Dev.* 2009; 8: 1-6.
8. Chandan M, Chandana P, Mammavathy D, Srikanth D, Rahila T. Needle-free drug delivery systems: a review. *Int J of Pharma Research and Dev.* 2011; 3:8-9.
9. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. *Nat Rev Drug Discov.* 2006; 5:543-548.
10. Jackson LA, Austin G, Chen RT, Stout R, DeStefano F, Gorse GJ, Newman FK, Yu O and Weniger BG. Safety and immunogenicity of varying dosages of trivalent inactivated influenza vaccine administered by needle-free jet injectors, *Vaccine.* 2001; 19:4703– 470.
11. Bakshi P, Roy S, Sadhukhan S, Maiti S. Painless Microneedles for Intradermal delivery of Vaccines; *J. Adv. Pharm. Edu. Res.* 2014; 4(2): 158-164.
12. Reis EC, Jacobson RM, Tarbell S and Weniger BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. *Pediatr Ann.* 1998; 27:375-386.
13. Kumar RB. Needle Free Injection Systems, *International Journal of Pharmaceutical, Chemical and Biological Sciences,* 2012;1(9):57-72.
14. Chavan B, Doshi A, Malode Y, Misal B. Review on needle free drug delivery systems, *Int J of Pharma Research and Review,* Sept 2013; 2(9):30-36.
15. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. *Nat Rev Drug Discov.* 2006; 5:543–548.
16. Almond GW, Roberts JD. Assessment of a needleless injection device for iron dextran administration to piglets. *IPVS Proc.* 2004:618.
17. Senn MK, Bradford JR, Cook DL, Loskutov A. Comparison of pharmacokinetic parameters for Excenel RTU when injected by needle or Felton Pulse 250 needle-free injector. *AASV Proc.* 2004: 263-265.
18. Evans A. Intra-dermal vaccination series. Part 2. Original engineering solution. *Pig Progress.* 2006; 22:30.

19. Aguiar JC, Hedstrom RC, Rogers WO, Charoenvit Y, Sacci JB, Lanar DE, Majam VF, Stout RR, Hoffman SL. Enhancement of the immune response in rabbits to a malaria DNA vaccine by immunization with a needle-free jet device. *Vaccine*. 2001, 20:275-280.
20. Anwer K, Earle KA, Shi M, Wang J, Mumper RJ, Proctor B, Jansa K, Ledebur HC, Davis S, Eaglstein W, Rolland AP. Synergistic effect of formulated plasmid and needle-free injection for genetic vaccines. *Pharm. Res.* 1999, 16:889-895.
21. Reis EC, Jacobson RM, Tarbell S, Weniger BG. Taking the sting out of shots: control of vaccination-associated pain and adverse reactions. *Pediatr. Ann.* 1998, 27:375-386.
22. Royer G, Charreyre C, Milward F. Efficacy and safety of needle-free transdermal delivery of a novel *Mycoplasma hyopneumoniae* bacterin. *AASV Proc.* 2006, 239-241.
23. Grosenbaugh DA, Leard T, Pardo MC. Comparison of the safety and efficacy of a recombinant feline leukemia virus (FeLV) vaccine delivered transdermally and an inactivated FeLV vaccine delivered subcutaneously. *Vet. Ther.* 2004, 5:258-262.
24. Jones GF, Rapp VG, Wilke R, Thacker EL, Thacker BJ, Gergen L, Sweeney D, Wasmoen T. Intradermal vaccination for *Mycoplasma hyopneumoniae*. *J. Swine Health Prod.* 2005, 13:19-27.
25. Jamin A, Gorin S, Le Potier MF, Simon GK. Characterization of conventional and plasmacytoid dendritic cells in swine secondary lymphoid organs and blood. *Vet. Immunol. Immunopathol.* 2006, 114:224-237.
26. Ekwueme DU, Weniger BG, Chen RT. Model-based estimates of risks of disease transmission and economic costs of seven injection devices in sub-Saharan Africa. *Bull World Health Organ.* 2002, 80: 859-870.
27. Romani N, Clausen BE, Stoitzner P. Langerhans cells and more: langerin-expressing dendritic cell subsets in the skin. *Immunol Rev.* 2010, 234: 120-141.
28. Vien NC, Feroldi E, Lang J. Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children. *Trans R Soc Trop Med Hyg.* 2008, 102: 294-296.
29. Reddy MS, Kumar MR, Kumar S, Goli A, Kumar S. Review on Needle free drug delivery systems, *International Journal of Review in Life Sciences.* 2011, 1(2), 76-82.
30. Kolhe S, Sontakke S. A Review on needle free drug delivery system, *International journal of current pharmaceutical research.* 2013, 5(2), 20-28.
31. King T. A review of needlefree injection technologies. In World Pharma Web Pharma Ventures, Ltd. 2001; 1-5.
32. Zsigmond EK, Darby P, Koenig HM, Goll EF. Painless intravenous catheterization by intradermal jet injection of lidocaine: a randomized trial. *J. Clin. Anesth.* 1999, 11, 87-94.
33. Saravia ME, Bush JP. The needleless syringe: efficacy of anaesthesia and patient preference in child dental patients. *J. Clin. Pediatr. Dent.* 1991, 15, 109-12.
34. Brodell RT, Bredle DL. The treatment of palmar and plantar warts using natural alpha interferon and a needleless injector. *Dermatol. Surg.* 1995, 21, 213-18.
35. Suzuki T, Takahashi I, Takada G. Daily subcutaneous erythropoietin by jet injection in pediatric dialysis patients. *Nephron* 1995, 69, 347.
36. Varley PG, Uddin S, Hlodan R, Edwards S, King T. Monoclonal antibody injection without a needle. *Br. J. Pharmacol.* 2000, 131, 218.
37. Suhonen TM, Bouwstra JA, Urti A. Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations. *J. Controlled Release.* 1999, 59, 149-61.
38. Tangri P, Khurana S. Drug Delivery via Painless Injection: Needle free Injection Technology. *International journal of drug formulation and research.* 2011; 2(5), 26-32.
39. Patni P, Varghese D, Balekar N, Jain DK. Needle free insulin drug delivery, *Indian journal of Pharmaceutical sciences.* 2006; 68(1): 7-12.