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Review Article

A REVIEW ON NEEDLE FREE DRUG DELIVERY SYSTEM

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ABSTRACT

Needle-free injection systems are novel ways to introduce various medicines into patients without piercing the skin with a conventional needle. They can take the form of power sprays, edible products, inhalers, and skin patches. Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. It is anticipated that these systems will increase the incidence of vaccination and reduce the amount of prescribed antibiotics. Moreover, they should reduce the number of needle stick accidents that have resulted in some health care workers contracting diseases. Today, they are a steadily developing technology that promises to make the administration of medicine more efficient and less painful. Companies are still working on producing devices that are safer and easier to use. They are also working on alternatives which can deliver even more types of medicines.

There appears to be tremendous opportunity for needle-free technology to have major impact in the industry. It is likely that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts needle free technology and demonstrates it as needle free injections which are well being supported by organizations like WHO and CDC (Centre for Disease Control).

Keywords: Needle free devices; Needleless injection; Powder jet.

INTRODUCTION

The main goal for the delivery of any drug therapy is oral administration with once or twice daily dosing. However, there are large numbers of therapies protein-based, gene-based and vaccine-based that cannot be delivered by this route for example insulin, growth hormones and other similar biologics. The pitfalls of needle-based injections are psychological resistances to self-injection or needle-phobia, awareness of serious problems has caused physicians and their patients to either delay therapy initiation or seek out less-invasive alternatives and even at some cost to clinical effectiveness.

To overcome the problems related to needle based injections, there is one technology that has received considerable attention during the past few years and that offers all of the sought after benefits is—Needle Free Injection Technology (NFIT). These technologies have been developed for injecting liquid formulations, as well as injecting drugs and vaccines in a solid dosage form.

This technology was first described in the 19th century in France, when the French company-H Galante-manufactured an 'apparatus for aquapuncture'. It was first commercialised in the US in 1960s. Bioject had summed up the reasons for it in their brochure stating "Patients hate needles, healthcare professionals fear accidental needle stick injuries, drug companies are looking for new and innovative ways of delivering their products.

PowderJect Pharmaceuticals one of the first companies to develop a needle-free technology for injecting powdered drugs into the skin. As long as drugs have been known to cure diseases, people have searched for better methods of delivering them.[1,2]

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. The design of the device has a major influence on the accuracy of subcutaneous delivery and the stresses imposed on the product to be delivered. When a needle is inserted through the skin, the vaccine or drug it carries provides systemic immunity. This is because the vaccine gets into the bloodstream and provokes the body to create antibodies that are carried throughout the entire body.

Needle-free systems are designed to solve these problems making them safer, less expensive, and more convenient. It is anticipated that these systems will increase the incidence of vaccination and reduce the amount of prescribed antibiotics. Moreover, they should reduce the number of needle stick accidents that have resulted in some health care workers contracting diseases.[3,4,5]

STRUCTURE OF SKIN

Knowledge of the structure of skin is essential for successful administration of drugs through needle free injection systems as these drugs are administered underneath the skin. Human skin is generally made of two layers i.e., epidermis and dermis. (Fig 1)

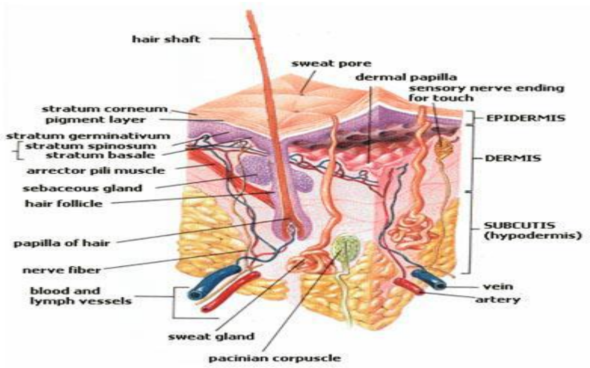

Fig. 1: Human Skin

Epidermis: It is the outmost layer of the skin. It forms the waterproof, protective wrap over the body's surface and is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis. The main type of cells which make up the epidermis are Merkel cells, keratinocytes, melanocytes and Langerhans cells are present. The epidermis can be further subdivided into the following strata (beginning with the outermost layer): corneum, lucidum (only in palms of hands and bottoms of feet), granulosum, spinosum, basale.

Dermis: The dermis is the layer of skin beneath the epidermis that consists of connective tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane.

It also harbors many mechanoreceptors (nerve endings) that provide the sense of touch and heat. It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. 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.

Hypodermis: The hypodermis is not part of the skin, and lies below the dermis. 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. The main cell types are fibroblasts, macrophages and adipocytes (the hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body. Another name for the hypodermis is the subcutaneoustissue.[6]

Advantages

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 effect of shear.
5. Provide rapid delivery and reproducibility comparable with needle & syringe.
6. Improve bioavailability over other non- 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.
10. It is trouble free, simple, self-administered.
11. Low sensation and safety .
12. Solid dosage forms can be administered .
13. Minimal skin response and no bleeding or bruising .
14. Excellent dose response is observed with increased drug doses.
15. Bio-equivalence has been demonstrated enabling the development of generic drugproteins.

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[7,8] .

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 ultra-fine stream of high-pressure fluid that penetrates the skin without using a needle. The design of the device has a major influence on the accuracy of subcutaneous delivery and the stresses imposed on the product to be delivered. The design must ensure that a sufficiently high pressure is generated to puncture the skin, while the subsequent pressure is reduced to ensure that the molecule is deposited comfortably at a level that does not reach the muscle tissue (fig.2).

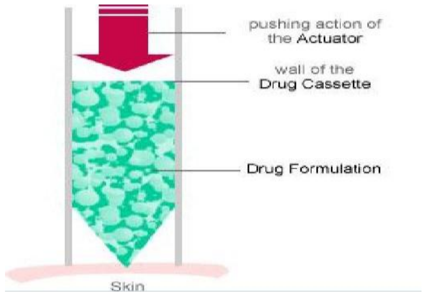

Fig. 2: Mechanism of Working

High-pressure delivery could potentially damage fragile molecules, such as monoclonal antibodies. Successful delivery of such molecules, therefore, requires a device with carefully controlled power **nuance**s. Several companies are involved in development of this technology, which includes, Antares Pharma Inc, Aradigm Corporation, Bioject Medical Technologies Inc and Biovalve Technologies Inc.[9]

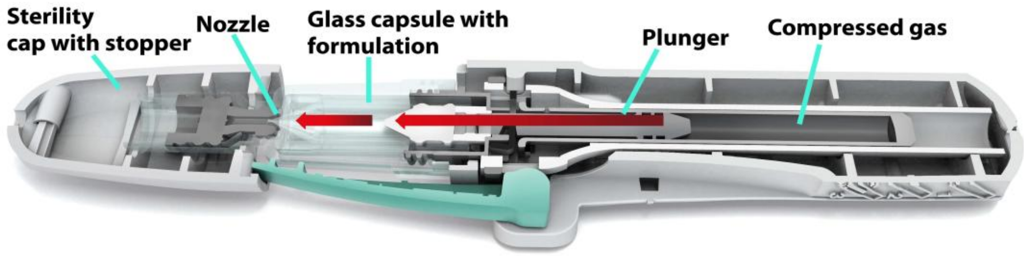

Fig. 3: Design of needle less injection device

DESIGN OF A NEEDLE LESS 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.3). 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.[9]

Types of needle free drug delivery system

Needle-free technologies can be broadly separated into three types

1. Powder injections.
2. Liquid injections.
3. Depot (or projectile) injections.

All work on the same basic principle of delivering medication by pressurised contact of fluids with the skin.

1. Powder injectors

Mechanism: 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).

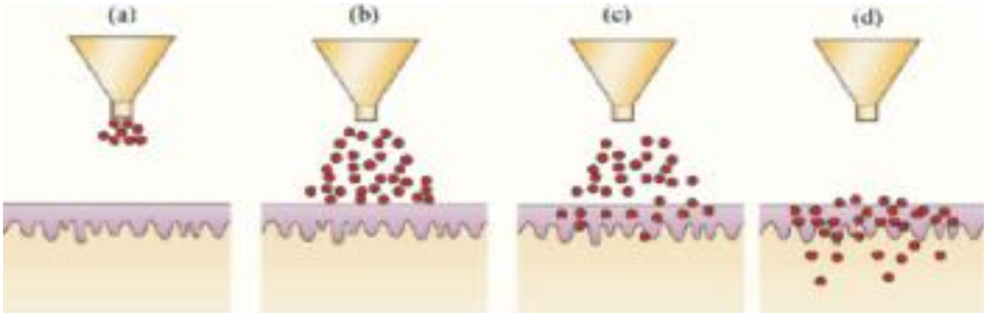

Fig. 4: Drug delivery using powder injector

(a) Ejection of particles from nozzle.

(b) Impact of particles on skin surface of jet on skin surface, development of hole inside skin with progress of injection.

(c) Deposition of drug at the end of hole in an earspherical or hemispherical pattern (spherical pattern shown) and 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.

Another design used for studying powder injection mechanisms is light gas gun, which uses an accelerating piston for imparting desired particle velocity. Upon triggering the actuation mechanism; the piston accelerates and carries the particles with it. A deceleration mechanism forces the piston to slow down and makes the particles leave the surface of piston. The particles are ejected and they impact on target tissue surface.

2. Liquid injections

The basic principle of this injection is "if a high enough pressure can be generated by a fluid in intimate contact with the skin, 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.

Mechanism: The basic design of commercial liquid jet injector consists of a power source (compressed gas or spring), piston, drug-loaded compartment and a nozzle with orifice size typically ranging between 150 and 300m. Upon triggering the actuation mechanism, the power source pushes the piston which impacts the drug-loaded compartment, there by leading to a quick increase in pressure. This forces the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200m/s. A schematic of injection process is show in Fig. The jet is turbulent in nature and the diameter of the jet is comparable to that of the orifice but increases with distance travelled. Upon implunging on skin, the jet punctures through the skin and initiates hole formation. 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 micro seconds. As the jet progresses deeper in the skin, velocity decreases until it does not have sufficient energy to continue hole formation. This completes the first phase of injection i.e. unidirectional skin puncture and is followed by these second phase, multidirectional jet dispersion from the end point of penetration. Further, the dispersion of liquid from this point appears to be approximately hemispherical, whose shape is governed by jet power (fig.5).

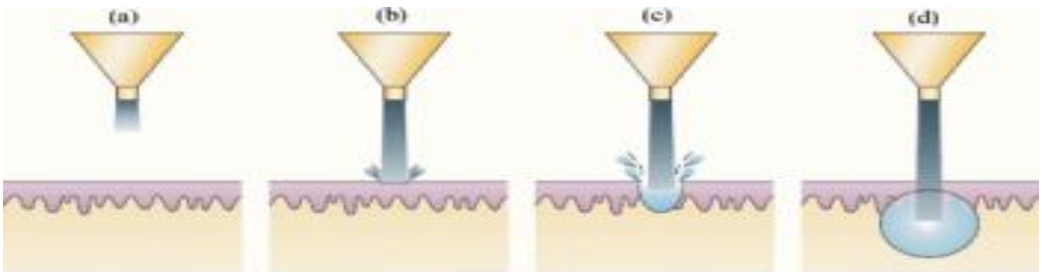

Fig. 5: Schematic of drug delivery using liquid jet injector

Sequential steps are

(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 hemi spherical pattern .

3. 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.[10]

Needle free insulin delivery

Putting up with needle pricks to avoid the complications of diabetes may seem a small price to pay. But injections can be daunting for children and those newly diagnosed with diabetes - and can be simply terrifying for those with a phobia of needles. Injecting using modern day needles is relatively painless, but some still find it unpleasant. There can be side-effects like bruising or bleeding from the injection sites. Also patients are advised to rotate where they inject because repeated jabs can cause noticeable lumps and dips in underlying fatty tissue, known as lipohypertrophy and lipoatrophy. With medical advances that bring us treatments for the previously incurable, surely there must be a better way.

Needle-free insulin delivery is the Holy Grail of diabetes treatment that scientists have been seeking for at least last 60 years. Some new approaches have reached the market, and others are not far behind. Others remain in the laboratory, but promise to revolutionize diabetes management.[11-15]

Jets: The way to get insulin through the skin and into the bloodstream is to use a pressurized jet. Insulin jet injectors have been available on the market for decades now. By forcing the insulin through a specially designed nozzle, they produce a very fine and highly pressurized stream of insulin that is able to penetrate the skin without a needle. But despite no needle, this method is not entirely pain-free. [16-18]

CURRENT NEEDLE FREE DEVICES IN THE MARKET

Mhi-500

Mhi-500 is the novel needle free insulin delivery system which offers benefits for all those involved in diabetes care and also for those involved in the management of clinical waste. It is a real alternative to needle based delivery systems. Compared with a needle injection system, the mhi-500 needle-free insulin delivery technology improves the dispersion of the insulin throughout the tissue. This technology achieved the Food and Drug Administration (FDA) approval in 1996 for the subcutaneous delivery of insulin. This system has been used to give thousands of successful injections without the use of a needle. The mhi-500 injects insulin by using a fine, high pressure jet of insulin. 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.

Recojet

Shreya Life Sciences has recently launched its recombinant human insulin under the brand name Recosulin and a needle free insulin delivery device, Recojet. According to the company sources, Recojet is India's first needle free insulin delivery device and poised to revolutionize the insulin therapy. The new device is expected to give a boost to the therapy, as needle phobia was one of the reasons preventing insulin use on a wider scale. 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.

Table 1: Needle less injection devices on the market product

	Company	Actuation method	Depth of penetration	Drug types	Drug volume (ml)	Comments
Biojector 2000	Bioject	Compressed gas	Intramuscular, Subcutaneous.	Liquid	1	Used to deliver vaccines.
Vitajet3	Bioject	Spring	Subcutaneous	Insulin	0.02-0.5	Can be used for self administration
Iject	Bioject	Compressed gas	Intramuscular, Subcutaneous Intradermal.	Liquid	Variable	Available for single use or multiple use.
Injex30	Injex	Spring	Subcutaneous	Insulin	0.05-0.3	Dual safety system is present.
Injex50	Injex	Spring	Subcutaneous	Insulin	0.1-0.5	Delivers larger dose than injex30.
Injex150	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	Delivers drug in less than 60 milli sec.
Miniject	Bio valve	Compressed gas	Intramuscular, Subcutaneous, Intradermal.	Liquid	0.1-0.3	Can deliver wide range of drugs.
Crossject	Crossject	Spring	Intramuscular, Subcutaneous, Intradermal.	Liquid	0.2-1	Operating is based on novel gas tech.
Penjet	Penjet	Compressed gas	Intramuscular, Subcutaneous, Intradermal.	Liquid	0.1-0.5	Low cost, easy to operate

Biojector 2000

The 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.

The Biojector 2000 uses sterile, single-use syringes for individual injections, which prevent the cross contamination that has been reported with fixed nozzle jet injection systems. More than 10 million injections have been administered successfully using the Biojector 2000, with no reports of major complications. Because there is no needle, the Biojector provides healthcare workers with an unparalleled level of protection against accidental needlestick injuries. 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.

Vitajet 3

The Vitajet 3 is an easy-to-use, economical needle-free injection system for delivering insulin. The system requires no maintenance or re-assembly. 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 exclusive, easy-to-read Crystal Check disposable transparent nozzle allows inspecting the dosage prior to injection and visually confirming loading and full discharge of your insulin after each use. 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.

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 customized version of Bioject's Vitajet 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.

SeroJet

The SeroJet is a needle-free injection system for delivering Serostim recombinant human growth hormone for treatment of HIV-associated wasting in adults. HIV-associated wasting is a metabolic condition in which people infected with HIV lose body weight. If not treated, this could result in increased morbidity and mortility.

Serono developed Serostim to treat this condition by utilizing the natural properties of growth hormone in increasing lean body mass. SeroJet is a customised version of Bioject's Vitajet needle-free injection system. The system includes customized dosage features to accurately deliver variable doses of Serostim. The SeroJet received FDA market clearance for delivering subcutaneous injections of Serostim in March 2001.

Iject

Bioject has developed a second-generation gas-powered injector known as the Iject, which is based on the design and performance of the B2000 and is intended to serve as a single-use pre-filled device. The pressure profile of the Iject has been documented by in vitro testing to be virtually the same as that of the B2000, and injection performance of the two devices is therefore predicted to be equivalent. 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 distributed "ready to use." Thus, it requires no additional parts or modifications for function. The device is primed by rotating the trigger sleeve 180º, and an injection is administered by advancing the trigger sleeve while the nozzle is held against the injection site. The Iject needle-free injection system is an investigational device, subject to the US Food and Drug Administration clearance for commercial distribution.

Mini-Ject

The Mini-Ject represents the next generation in needle-free injection systems by combining the features of accuracy reliability, a variety of pre-filled options, comfortable administration, and full disposability, all within a patient friendly easy-to-use design. The Mini-Ject can deliver a wide range of drugs, ranging from small molecules to large proteins, fragile antibodies, and vaccines. Delivery can be targeted to intradermal, subcutaneous or intramuscular depending on the clinical need. 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.[19-20]

Applications of needle free injection technology

1. Intraject (Weston medical) technology used to deliver drugs including proteins, peptides, monoclonal antibodies, small molecules and vaccines.

2. Medi-Jector vision (Antares Pharma, lnc.) technology used to create a micro thin stream of insulin that penetrates the skin.

3. Powderject(Powderject pharmaceuticals) technology delivered inulin to hairless guinea pigs, delivery of large macromolecules across the skin, used for intradermal DNA immunization against influenza a virus in mice.

4. Jet injectors' technologies deliver proteins such as Β- interferon as well as small organic conventional therapeutic agents such as lidocaine (lignocaine) for local anaesthesia.

5. The Disposable Syringe Jet Injector (DSJI) Project is supporting clinical research on the delivery of vaccines with jet injectors. [21,22]

CONCLUSION

Needle free technology offers the very obvious benefit of reducing patient concern about the use of needle. Additional benefits include very fast injection compared with conventional needles and no needle disposal issues. Not only it can benefit the pharmaceutical industry in increasing product sales, it has the added potential to increase compliance with dosage regimens and improved outcomes. In the developing world, there are major challenges of disease transmission through re-use of needles. Organisations 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. The biotech revolution is bringing in a range of protein-based therapeutics into the market place at rapid pace more than 300 products in active development. These protein-based therapeutics especially monoclonal antibodies (MAbs), which are anticipated to represent 30 per cent of pharmaceutical sales by 2007 and which are otherwise challenging to deliver non-invasively, will continue to be formulated as injectables. There appears to be tremendous opportunity for needle free technology to have major impact in the industry. It is likely that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts needle-free technology and demonstrates its versatility, acceptance and value in major therapeutic area.

Increased awareness and patient acceptance is expected to play a crucial role in the market penetration of the needle free technology. 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 demonstrated consistent delivery to epidermis, the dermis and the subcutaneous layer and the intramuscular space. While the question remains over the ability of this technology to target the dermis or the muscle across a very wide range of subject morphologies, published data suggest that the delivery is at least as good as that achieve with the needle which remains the gold standard for all the parenteral injections.

REFERENCES

1. Chandana P, Mannavathya D, Srikant D. Needle Free Drug Delivery System: A Review. International Journal of Pharmaceutical Research and Development 2011; 3(7):7-15.
2. http://www.worldpharmaceuticals.net
3. Seth GL. Bihani SD. An evolutionary approaches in development of needle free injection technology. International journal of pharmacy and pharmaceutical sciences.2012; 4(1): 590-596.
4. Stachowiak JC, Li TH, Arora A,Mitragotri S , Fletcher DA. Dynamic control of needle-free jet injection. Journal of Controlled Release .2009; 135: 104–112.
5. http://www.pharmatechnology.com
6. Tortora G, Derickson B. Principles of Anatomy and Physiology.11th ed. John Wiley & Sons. 2008:145-151.
7. Reddy SM, Ranjith KM, Kumar KS, Goli A, Kumar PS. Review on Needle free drug delivery systems. International Journal of Review in Life Sciences 2011; 1(2): 76-82.
8. Daniels CS, Headquarters CH. Needle-Free Injection-Pros and Cons. High Plains Dairy Conference Amarillo, Texas; 25-36.
9. http://www.marketresearch.com
10. Jagannathan S, Chaansha S, Rajesh K, Santhiya T, Jayaraj D, Ayyappan SR. A novel approach in delivering Immunobiologicals : A Glimpse. Advanced Biotech. 2009: 22-31.
11. Pandey Shivanand, Patel Jigisha, Patel Kinjal: Various emerging Technologies in Insulin Delivery System. International Journal of Pharma Research and Development 2009; 8: 1-6.
12. http://www.ondrugdelivery.com
13. Chauhan NS, Chauhan S, Handa V, Arora A,Singh V. Recent Advances in Insulin Delivery Systems: An Update. World Applied Sciences Journal 2010; 11(12): 1552-1556.
14. Patni P, verghise D, Balekar N, Jain DK. Needle free insulin drug delivery. Indian Journal of Pharmaceutical Sciences 2006; 68(1):7-12.
15. http://www.pharmatutor.org

16. Chase CL, Daniels CS, Garcia R. Needle-free injection technology in swine: Progress toward vaccine efficacy and pork quality. Journal of Swine Health and Production 2008; 16(5):254–261.
17. Khyati SJ, Patel RP, Asari VM, Prajapati BG. Recent Advances In Vaccine delivery. Journal of Applied Pharmaceutical Science.2011; 1(1): 30-37.
18. Giudice EL, Campbell JD. Needle-free vaccine delivery. Advanced Drug Delivery.2006; 158: 68–89.
19. Vishnu P, Sandhya M, Sreesh KR, Vani CV. Review on needle free drug delivery system. International journal pharmacy.2012; 2(1): 148-155.
20. Harrison RG. Needle Free Drug Delivery Technology. Innovations in Pharmaceutical Technology; 3(2):60-63.
21. http://www.nap.edu
22. http://www.cdc.gov