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NEEDLE-FREE INJECTIONS: A GENTLE APPROACH TO HEALTHCARE

[1]K. Navaneetha, [2]SK. Sushma Taj, [3]M. Deepika, [4]K. Jahnavi, [5]B. Jeshma Kalyani
[1,3,4,5]Research Students, [2]Assistant Professor, Department of Pharmaceutics,
Joginpally B.R. Pharmacy College, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India.

Abstract: This comprehensive review explores the evolution, mechanisms and applications of needle-free injection technology in drug delivery. Beginning with a historical overview, tracing back to 1853 invention of the syringe, it progresses to the present, encompassing various needle-free devices such as skin patches, inhalers and power sprays. The intricate structure of human skin is discussed, emphasizing the importance of understanding its layers for effective drug delivery. The classification of needle-free injection technology is presented based on working principles, type of load, mechanism of drug delivery, and site of delivery. Various technologies, including spring systems, laser-powered devices, energy-propelled systems and shockwaves, are analyzed in detail. The article delves into the challenges associated with gas-propelled systems, emphasizing the need for pressure regulation and innovative solutions. The mechanisms of liquid, powder and projectile/depot delivery methods are elucidated, providing insight into their applications and limitations. Further exploration covers nano-patches, sandpaper-assisted delivery, iontophoresis, and micro-needles, each offering distinct advantages in drug delivery. The review details the working stages of needle-free drug delivery, highlighting the phases of peak pressure, delivery, and drop-off. Components of the injection device, including the injection device, nozzle and pressure source, are dissected, offering a comprehensive understanding of the technology. Examining specific needle-free injection devices such as Serojet, Iject, Injex, and Bioject® Zetajet, the review concludes with a discussion on the advantages and disadvantages of needle-free injection technology. The potential benefits, including painless injections, enhanced patient adherence, and reduced risk of contamination, are weighed against challenges like needle phobia and potential overdose risks, providing a balanced overview of this innovative drug delivery approach.

Keywords: Needle-free drug delivery, Jet injection, Micro-needle patches, Iontophoresis, Gas-powered injection, Spring-loaded injector.

I) Introduction:

The term "needle-free" refers to a broad category of drug delivery technologies, including those that employ electrophoresis instead of a needle to transport medications through the skin and those that use one or more tiny needles. Devices without needles include skin patches, inhalers, edibles, and power sprays. Devices are available for use at home or in a doctor's office, in versions for numerous patients, and for institutional usage. They are also available in disposable and reusable forms. [1]

II) History:

The development of needle-free devices and syringes has been crucial to the advancement of medicine and healthcare. French physician Charles Gabriel Pravaz created the first syringe in 1853. The fundamental architecture of syringes has not altered in the past 150 years, not with-standing a few small advancements in technology since then. In 1936, Marshall Lockhart introduced needle-free devices in his jet injection patent. Higson and associates invented high-pressure "guns" in the early 1940s, which punctured the skin with a tiny liquid jet and injected the medication into the tissues beneath. Improved patient care and a revolution in medicine have resulted from the ongoing development of syringes and needle-free devices. [2]

III) Structure of Human Skin:

Typically, human skin consists of three layers. They are:

1.The epidermis

2.Dermis.

3. Hypodermis

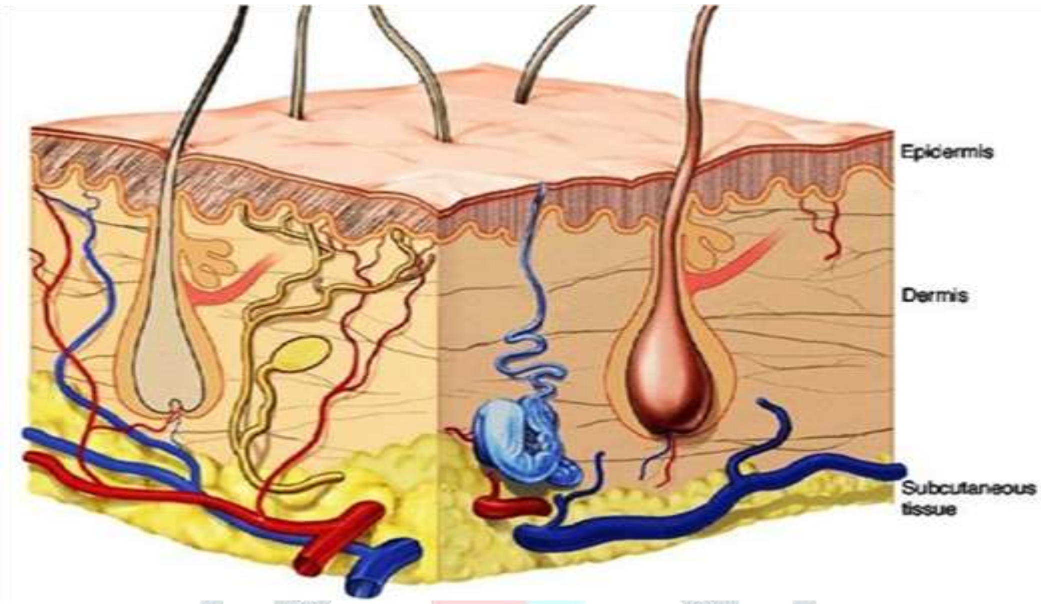

fig1: structure of human skin [10]

1. Epidermis:

It is the outermost layer of skin and is mostly made up of layers of melanocytes, keratinocytes, Langerhans cells, and Merkel cells. It serves as a barrier that separates the body from the outside world both chemically and physically. The nature of the epidermis is stratified squamous epithelium. [3,4,5,6]

Its four layers are as follows:

1. Stratum basale

2. Stratum spinosum

3. Stratum granulosum

4. Stratum corneum

2. Dermis:

It is the region of the subcutis and epidermis' supporting connective tissue. Sweat glands, hair roots, nerve cells and fibres, blood vessels, and lymph vessels make up the majority of the dermis. It is mostly made up of a thicker reticular layer and thin papillary layer. Its primary purpose is to shield the body from pressure and stress. The mechanoreceptors in the dermis provide a sense of touch and heat. [3,4,5,6]

3. Hypodermis:

It is the layer that is underneath the dermis and consists of fat and loose connective tissue. Its function is to attach the skin to the underlying bone and muscle and to provide blood vessels and nerves to the area. [3,4,5,6]

IV) Classification of needle free injection technology: [7,8]

1**. On the basis of working**

- Spring systems
- Laser-powered
- Energy propelled systems
- Lorentz force
- Gas propelled/air forced
- Shockwaves

2. On the basis of the type of load

- Liquid
- Powder
- Projectile

3. **Based on drug delivery system**

- Nano-patches
- Sandpaper assisted delivery
- Iontophoresis enabled
- Micro-needles

4. Based on the delivery site

- Intradermal injectors
- Intramuscular injectors
- Subcutaneous injectors

1. On the basis of working:

a) Based on a functional spring system:

Springs have been used as energy reservoirs in devices that use needle-free injection technology. One of the easiest and most direct ways to use needle-free injection technology is to store energy and then transfer it farther using a spring. However, the spring's design must follow conventional processes, and the storage conditions must be straightforward to avoid the spring taking a "set" over time and affecting the device's performance. According to Hook's rule, the force a spring delivers will decrease according to the distance the load is delivered, which poses a basic design flaw. In other words, with spring-assisted needle-free injection technology, the pressure will gradually decrease during the injection process. [9]

b) Laser-powered:

Prof. Jack Yoh and his colleagues have created a more advanced version of needle-free injection technology that uses a laser-based device to shoot tiny medication jets into the skin. The device drives an extremely fine and exact stream of medication or drug with the appropriate amount of force using an erbium-doped yttrium garnet laser, the same laser used in skin resurfacing procedures. The medication to be supplied is held in place by an adaptor that is built into the laser. The apparatus furthermore incorporates a water chamber for the purpose of propelling the medication; nevertheless, the configuration is such that the drug is isolated from the propellant (water) via a membrane. [9]

c) Energy propelled system:

In addition to being frequently noisy and occasionally uncomfortable, commercial spring-powered jet injectors provide little to no control over the pressure used to provide the medicine during the injection. Energy can also be produced in other sources to provide the force needed to propel the medication in order to have a penetrating effect.

d) Lorentz force:

A needle-free injection system developed by MIT researchers employs Lorentz force to propel a piston forward, ejecting the medication at a very high pressure and velocity (almost as fast as sound in air). The Lorentz force actuator, which powers the entire mechanism, is the device's primary component. [9]

e) Gas propelled/air forced:

Gas-powered needle-free injection technology has more potential because compressed gas has a higher energy density than a metal spring. However, gas-powered needle-free injection devices will be less suitable as a power source unless specific arrangements, design changes, or component modifications can be made to ensure that the pressure is kept, and the spring is replaced after every injection. Gas-powered devices typically require a periodic replacement of the gas cartridge or are single-use only. Developing a gas spring that retains a certain amount of gas to function while its shelf life is approaching is a significant task. Some devices use gas as a basic spring, where the stored gas accelerates the piston. These devices are portable and compact.

A different approach has been devised that employs carbon dioxide that has been liquefied at the pressure and temperature of storage to get around these problems. It has been demonstrated that this method works well because there is almost "no" or "zero" pressure loss with even a small gas leak from the container. The pressure in these containers doubles between 0 and 40 degrees, indicating that they are extremely temperature-sensitive. If the device's ideal operating temperature range is wider, this could have an impact on its performance.

A pressure regulator is a useful tool for solving this issue. The development of reusable, complex, and relatively more portable gas-powered needle-free injection technology has resulted from additional study. One such system, created by Team Consulting Ltd. in Cambridge, UK, uses a basic butane combustion engine to power the apparatus. Data must still be published and the system's overall effectiveness must yet be determined. The development of needle-free injection technology systems has involved major companies using a chemical method of gas generation, wherein the gas is created at a consistent and repeatable pace to power the device. The chemical "burns," producing gas, in a reaction that is started either physically or electrically. [10]

The primary disadvantages of this technology are:

- Difficult validation procedures.
- A bad smell brought on by the reactants burning.
- Production of reactants in large quantities.

f) Shockwaves: [11]

Anything that releases energy suddenly might cause shock waves. These disruptions have energy and have the ability to spread across a medium. Using this energy at supersonic speeds, researchers at the "Indian Institute of Science" (IISc) in Bengaluru have created a totally non-invasive medicine delivery device. The following are the main components of this device's prototype:

- A system of ignition to start the "charge."
- A polymer tube with an appropriate coating that holds the explosive substance.
- A chamber for loading drugs with drugs.
- The metal foils and cavity holder are also included in the system.

2. On the basis of the type of load Liquid:

a) Liquid:

The original form of needle free injection technology was liquid needle free injection technology, and major pharmaceutical companies are still developing this technique. The ability of a liquid jet, powerful enough to pierce the skin and the underlying fat layer without damaging the skin or the integrity of the drug molecule, is the key to the entire mechanism of achieving a successful injection with a needle-free device. Liquid needle free injection technology's mechanics are so intricate that new research has been done to comprehend the entire process. [12]

Fluid mechanics must be applied thoroughly when using needle-free injection technology to deliver fluid. The procedures that are involved are:

- **Registration:** The device's opening is positioned precisely over the skin's pores.
- **Exact pressure:** The ideal pressure for the fluid to be pumped at is one that is both strong enough to maintain the skin's holes open and consistent enough to prevent the holes from closing again.
- **Channel drilling:** The fluid's first pulse creates a deep enough conduit in the fat layer for the dose to drift into the skin from the hole. [13]

b) Powder:

The ability to manufacture particles of adequate density, accelerate them to a velocity powerful enough to pierce the skin and use enough of the particles in sufficient number to obtain the therapeutic dose levels are prerequisites for powder needle less injection. This was made possible by utilizing helium as a power source and changing the drug's formulation techniques. [14]

Drug transformation into hard particles having a diameter of 10–50 nm and a density roughly equivalent to that of a crystalline drug, either pure or in combination with excipients, coating the medication on gold spheres, which can serve as a few micrometer-diameter vector. This technique is mostly useful for DNA vaccinations. [15]

c) Projectile/depot:

The drug is processed into a long, thin depot with enough mechanical strength to transmit a driving force to a pointed tip, which may be formed of the medication itself or an inert material. This version of needle-free injection technology is highly advanced compared to earlier versions. A depot typically has the shape of a cylinder that is a few millimeters long and has a diameter of about 1 mm. The payload may be limited by this dimension, but there is still enough payload to support a large number of novel therapeutic proteins, antibodies, and other smaller molecules. When a sharp-tipped punch with a pressure of 3–8 mega Pascals (MPa) is applied, the depot is powerful enough to pierce the skin. It takes very few Newtons of force to prepare a depot of about 1 mm. As a result, the delivery mechanism would use energy transfer from an appropriate "spring" onto the depot. [16]

3. **Based on drug delivery system:**

a) **Nano-patches:**

Drug delivery via the skin using an applicator is necessary for the operation of a nano-patch or micro-projection. Since nano-patch projections cannot be seen with the naked eye, it is unlikely that they will cause individuals to become afraid. When it comes to vaccines, drug delivery by nanopatches has proven to be particularly effective. The entire procedure is painless, and nanopatches allow the vaccination to reach the important immune cells beneath the skin's surface.

b) **Sandpaper assisted delivery**:

In order to cause micro-derm abrasion, or the removal of the skin's surface layer, 220 grit "sandpaper" type of agent is typically rubbed onto the skin. This facilitates the entire drug delivery process. For cosmetic purposes, micro-derm abrasion has gained widespread acceptance. Drugs like lidocaine and 5-flurouracil can flow more easily through the skin when delivered with the help of sandpaper. Other forms of microderm abrasion have also been utilized to improve skin permeability. Vaccines against influenza and traveler's diarrhea have been created thus far with this method. (Clinical trials in progress). [17]

c) **Iontophoresis enabled:**

Numerous salts and other compounds are prevented from penetrating the skin due to its lipophilic composition. A little electric current of roughly 0.5 mA/cm2 is employed in iontophoresis to push several medication molecules through the skin. This technology uses two electrode patches to work; one serves as a drug reservoir and can be negatively or positively charged, depending on the substance, the other patch completes the circuit by being put somewhere else on the body. [18]

d) **Micro-needle**:

As the name implies, micro-needle patches use thousands of tiny spikes that are all about 750 µ long. The patches are applied to the skin and the spikes puncture the epidermis to administer the medication. The piercing is not deep enough to induce pain because it does not strike blood vessels or even pain receptors. Microneedles of different kinds, from plastic to complex metallic ones, have been produced. Some are hollow, filled with a liquid vaccination or formulation, while others are just "coated" with the medication. In addition to being incredibly successful, microneedle patches have also demonstrated improved patient compliance. Nevertheless, there are certain restrictions connected to the use of micro-needle patches. [19]

- Greater doses necessitate larger patches.
- The mixture needs to be able to "coat" or "stick" to the needle surface's spikes.
- The formulation must have needed the physicochemical characteristic to maintain a sharp tip for sufficient skin penetration if the needle is composed of the medication.
- Individual differences may exist in the microneedle's depth of penetration due to factors such as skin hardness, thickness, and application repeatability.
- The needle may become dislodged, by movements of the body or the body part to which the patch is placed. [20]

4. **Based on delivery site:**

a) **Intradermal injector:**

Utilizing these technologies, relatively more recent DNA-based vaccines have been administered to the intradermal layer. The system delivers the drug at a very shallow depth that is, between the layer of the skin. [21]

b) **Intramuscular injector:**

One of the most advanced needle-free injection technologies used to administer drugs intramuscularly. This technology delivers drugs in the deepest way possible. The most effective use of needle-free injection technology for drug delivery has been in immunization. [22]

c) **Subcutaneous injector:**

Through this technique, several therapeutic proteins, such as human growth hormones, have been delivered. The adipose layer, which is located just beneath the skin, receives the medication. [22]

V) Mechanism of working:

Needle-free injection method drives the vaccine through a tiny aperture at a fast speed using force produced by a compressed gas, usually N_2, CO_2 or air. The vaccine is delivered to the skin, subcutaneous tissue and intramuscular tissue in a split-second when it is administered through the skin by an ultrafine stream of fluid that permeates the epidermis. It takes less than 0.5 seconds for an injection event. [23]

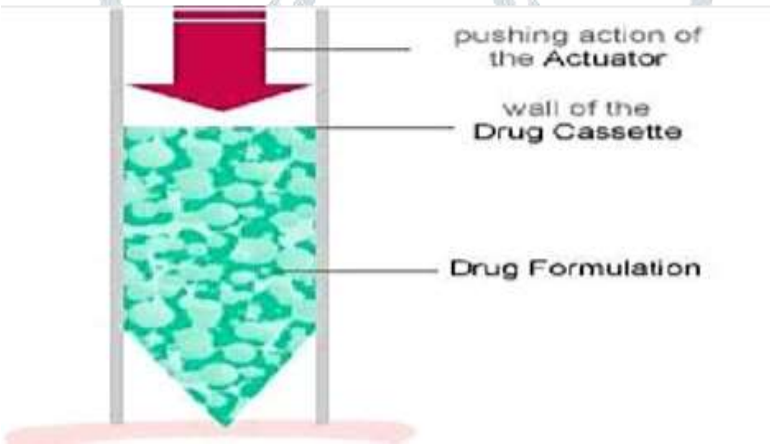

fig 2: mechanism of working of needle free injection system [23]

Stages of delivery:

The needle-free medication distribution process consists of three steps:

1. The phase of peak pressure, or ideal pressure needed to pierce skin (<0.025 sec)
2. Phase of delivery or dispersion (maximum 0.2 seconds)
3. Phase of drop-off (<0.05 sec)

To administer the vaccination, up to 0.5 seconds are needed in total. [24, 25, 26, 27]

Components:

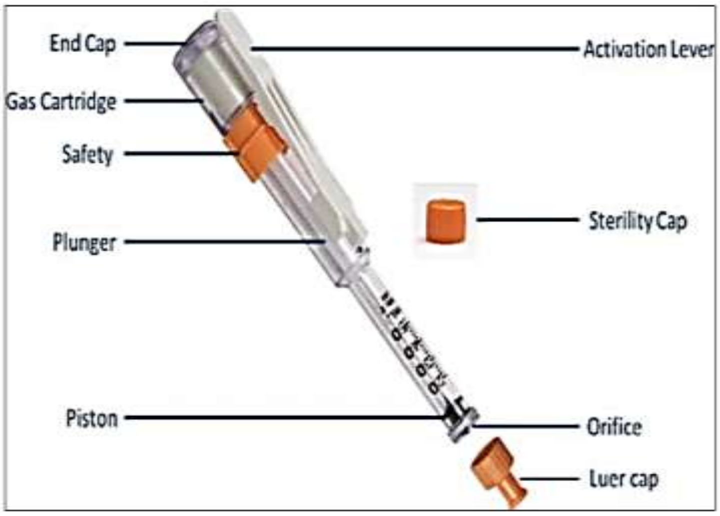

fig 3: components of needle free injection [28]

Component 1 - Injection device:

Its design, which incorporates a drug chamber, makes self-administration feasible. the device made of plastic. Sterile conditions are upheld all around the apparatus. A sterilized plastic syringe devoid of needles is included.

Component 2 – Nozzle:

The nozzle serves as the drug's conduit as well as the skin-contact surface. Through an aperture in the nozzle, the drug enters the skin during injection. The typical diameter of an opening is 100 µm. The nozzle discharges drug particles at a standard speed of 100 m/s, 2 mm deep. The most common orifice size, 0.127mm, corresponds to a 25-gauge needle. This makes the injection painless; all the patient feels, is a tap of gas across their skin, like when they flick their finger across their skin.

Component 3 - Pressure source:

It is essential for pushing a drug past the skin's surface and into the bloodstream. Storing energy in a spring and releasing it by pressing a plunger to provide the necessary pressure is one mechanical method for the pressure source. It might also be a pressure storage method, like the one depicted in fig 3, that uses gas cartridges filled with compressed gas.

The two gases most frequently employed in devices are nitrogen and carbon dioxide. Portable units generally have access to pressurized metal air cartridges. Device design has an impact on the product's stress level and the accuracy of medication distribution. The apparatus must guarantee the production of high pressure enough to pierce skin while protecting the medication molecule from damage. Fragile therapeutic molecules, such as monoclonal antibodies, are prone to destruction from high pressure. As a result, the design of a device may change based on the medication it is used for. Giving subcutaneous injections to little pigs involves lifting the loose skin in the flank or elbow region. This method is referred to as tenting. It is okay to inject SQ into the region directly behind the ear in sows. The traditional location for intramuscular injection is the neck, directly behind the ear. Injecting IM anywhere else is unacceptable as it will jeopardize the safety of the pig and it should never be injected into the loin or ham muscles. [29]

VI) Technologies:

1. Serojet:

The apparatus is intended for the subcutaneous delivery of Serostim, a recombinant human growth hormone. The Serojet apparatus is customized using Vitajet technology. The FDA approved this in March 2001 for marketing, and it is used to treat adult HIV-associated wasting. [30]

fig 4: serojet [30]

2. Iject:

The Bioject Company produces it as a gas powdered injection system of the second generation. A pre-filled, single-use, disposable injectable tool called the Iject is designed to give intramuscular or subcutaneous injections ranging from 0.5 to 1.00 ml. To activate the device, turn the trigger sleeve 180 degrees. The injection is given by pulling forward the trigger sleeve, where the nozzle is pressed up against the injection site. [31]

fig 5: iject [31]

3. Injex:

Local anesthetic can be administered via the Injex system. It is composed of an injectable ampoule with a 0.18 mm opening. The medication is injected at dosed pressure into the submucosa through this opening. The ampoule needs to be positioned 90 degrees on the attached gingiva, exactly above the tooth that needs to be anesthetized. About 0.3 mL is the maximum volume of local anesthetic that can be used. [32]

fig.6: injex [32]

4. Bioject®Zetajet:

The auto-disabling disposable syringe and the portable injector make up its two parts. It is designed to administer injectable drugs and vaccinations subcutaneously or intramuscularly. It is recommended for use by healthcare professionals as well as by people who self-inject at home. The special "auto-disable"function of the syringe assembly stops the syringe from being used again. [33]

fig 7: bioject [33]

5.Cool click:

It was created by Bioject to administer Saizen recombinant human growth hormone. Some children either create insufficient quantities of growth hormone naturally or none at all. In these situations, injections of Saizen or hormone replacement are necessary to sustain normal growth. [34]

fig 8: cool click [34]

6.Vitajet:

In 1996, the FDA approved it for commercialization. It is made up of disposable nozzles that are changed once a week and are used to subcutaneously inject insulin. [35]

7. Mhi-500:

Insulin is administered subcutaneously with this device. In 1996, the FDA approved the system for sale in all of Europe. Through the nozzle, the gadget injects a little stream of insulin into the subcutaneous layer of skin. [36]

8. Madajet:

It is frequently applied in dental care. It functions by discharging local anesthetic under pneumatic pressure. At the injection base, this stream forms a wheel that is between 5 and 6 mm in diameter. The apparatus delivers 0.1 cc intradermal injection volume per shot. [37]

VII) Types of needle-free injection systems: [38, 39]

Needles-free injection devices are not a new technology. The initial techniques were developed in the 1930s and were eventually used in numerous medical specialties. Changes and adaptations brought about by innovation and technology have increased the efficiency and accessibility of needle-free injection devices for users in general.

- Spring load jet injector
- Battery powdered jet injector
- Gas powdered jet injector

1. **Spring-load jet injector:**

The spring-loaded jet injector makes use of the drawn-back spring mechanism. Then a trigger is pressed to release the spring and inject a "jet stream" of medicine or vaccine into the dermal layers of the skin. It can be used subcutaneously, intramuscularly, or transdermally. After each spring-load activation, the spring must be manually repainted in order to treat the subsequent animal.

2. **Battery-powered jet injector:**

The dosage gear of the battery-operated jet injector is retracted by means of a compact, rechargeable battery pack. An electrical piston in the dosing device is automatically redrawn after each dosage. It reduces worker tiredness and is suitable for ongoing usage. A little trigger allows it to be released. The injector is similar to a hand drill that runs on batteries. Depending on the prescribed manner, the battery-operated system delivers the dosage by subcutaneous, intramuscular, or transdermal means.

3. **Gas-powered jet injector:**

The battery-operated jet injector uses a small rechargeable battery pack to retract the dosage mechanism. The electrical piston in the dosing mechanism automatically retracts after a dosage is given. It helps with continuous use and lessens worker fatigue. It is released by a little trigger. It appears to be a battery-operated hand drill. The battery-operated device administers the dosage subcutaneously, intramuscularly, or transdermally in compliance with the recommended procedure.

VIII) Design of needle free injection:

The three main parts of an air forced needle-free injection system are typically an air cartridge, a disposable needle-free syringe, and an injection device. A sturdy plastic is used to make the syringe, the injection tool. Because the syringe is the only part of the device that comes into contact with the skin, it is disinfected beforehand. The syringe is made in a way that requires disposal following each use.

A. Raw materials:

The materials used to make these devices must be pharmacologically inert, as they must come into close contact with the human body. Temperatures must not be above the materials' capacity while sterilizing them using heat. There exist various forms and dimensions for air forced injection systems. High strength and light-weight are the features of the thermoplastic, which makes them the choice of material to make these devices. Eg: Polycarbonate. Fillers are introduced in order to provide more stiffness to the polymer during molding. Plastics become stiffer, lighter, and more resilient as a result of the fillers. Colorants are incorporated into the plastic to alter its overall appearance.

B. The manufacturing process:

An injection system without a needle can be made in a variety of ways. The primary objective of the subsequent process is the development of an air-forced system. The meticulous process of molding the component pieces, assembling them and finally labeling and decorating the final product is how these systems are built. Usually, the needle-free injection system's manufacturer assembles the individual components after producing them off-site. Every production step is completed in sterile circumstances to prevent the transmission of disease.

C. Making the pieces:

First thing that needs to be done is to manufacture the plastic component parts from plastic pellets. The process is called injection molding. Plastic pellets are fed into a large holding bin on an injection moulding machine. They are heated to make a flow. The material is passed through, by a screw that is controlled hydraulically. The plastic is injected into a mold by means of a nozzle while the screw is rotating. The mould is composed of two metal components, that when combined, gives the shape. Once the plastic is in the mold, it is crushed for a predefined amount of time and then left to cool.

IX) Advantages: [28,40]

1. Less pain and stress to patients.
2. Elimination of needle disposal.
3. There are no circumstances in which a drug overdose or under-dose occurs.
4. It is ideal for individuals who experience needle-phobia.
5. It reduces the risk of skin punctures, damage, bleeding, bruising, and cause little skin reaction.
6. It enhances patient adherence, particularly when it comes to long-term medication delivery.
7. Since self-administration of injections is possible, there is no need to visit hospitals or specialists for injections.
8. There's no chance of cross-contamination from injuries caused by needle sticks.
9. It is possible to modify the depth and the quantity of medication administered.
10. Viscose liquids and powdered vaccines are both available for administration.
11. Because the medication is supplied as dry powder, its stability during storage is improved.

X) Disadvantages: [40]

1. High pressure delivery may cause injuries to skin.
2. No one size-fits all.
3. No guidelines for its disposal.
4. Chances of cros-contamination.
5. The detrimental effects of non-compliance in the long-term illnesses.
6. The increase in costs for in-patients needing injections at hospitals more frequently.

XI) Conclusion:

The evolution of needle-free injection technology signifies a transformative phase in drug delivery, from historical syringe development to diverse needle-free systems, advancements in various technologies. Understanding human skin structure is crucial as it influences the device design. Diverse drug delivery mechanisms, nano-patches, and innovative methods showcase deep research. Despite promises, challenges persist, which are addressed through ongoing R&D. Devices like Serojet and Iject exemplify practical applications, offering painless injections and patient benefits. However, challenges like cross-contamination and careful administration require continuous attention. In conclusion, needle-free injection technology holds promise, but addressing challenges is vital for safe adoption in medical practice.

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