Emerging trends in parenteral devices- Syringes and Needle-free injections

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ABSTRACT

The administration of the drug is possible through different routes like oral, Parenteral, etc. but for faster action and high bioavailability parenteral route is the most preferred one. The drug administration through the parenteral route requires a traditional syringe that is associated with some pitfalls like disposal problems, needle-based injury, contamination, reuse of needles, and needle phobia which need to be changed. Researchers reformed traditional needles and made many modified syringes like an auto disposable syringe and prefilled syringe. These syringes had eliminated the problem of disposability, reuse of needles, and needle-based injury up to a great extent. But the problem of needle phobia is still left so researchers developed needle-free injection technology which includes needle-free syringes and Nanopatches in which the drug is administered by a pressure-driven plunger. It also led to the self-administration of the drug. The review contains various advancements made in the syringes along with some applications.

Keywords: Parenteral, Syringe, Pre-filled syringe, auto-disposable syringe, Needle-free injection technology.

INTRODUCTION

Administration of drugs in daily life is always a challenging one, either it is oral administration or parenteral administration. Oral administration is the simpler method as compared to parenteral but the former is associated with certain limitations like the first-pass metabolism, uselessness at the time of dilemma, degradation of the drug in the stomach, administration to an unconscious patient, etc[2]. Oral administration to pediatric as well as geriatric is not an easy task[1]. But in the case of parenteral dosage there is no first-pass metabolism as it is directly administered in blood. Parenteral dosage forms are always administered comparatively in low doses as no drug is metabolized in the liver. But the administration of the drug by parenteral route is not possible without using any device. The devices made for parenteral drug administration are known as parenteral injecting devices but it has its own advantages as well as disadvantages. The difficulty of using injecting device is one of the major disadvantages and to overcome this, pharmaceutical industries are focusing more and more on the ease of using the device. Another problem associated with it is the administration of a drug by parenteral route require healthcare professional especially in case of patients suffering from certain chronic diseases like diabetes, rheumatoid arthritis, multiple sclerosis, etc[4]. Patient cannot go three times a day to health workers for parenteral drug delivery. Device design is another characteristic on which the manufacturer focuses on; good device design guarantees good usability. The device has a size bigger than hand or non-grippable design can make the patient prone to the fatal accident which correspondence to negative safety outcome. The device design should be as per user need. For example, in the case of an insulin pen, the design should be like a traditional pen which denotes that

the needle is at the cap side and one has to hold it from the opposite direction. The regulatory authority had also issued a written document for manufacturing of injecting devices to ensure patient safety during self-administration. Another problem associated with the parenteral device is its disposability. The parenteral device should always be disposable as non-disposable devices that can result in the spreading of the infection like hepatitis B, hepatitis C, and HIV. Disposal of the syringe and other devices is a very difficult as well as life-threatening issue. The devices used in hospitals and other medical camps submit the devices to governing disposing authority but the devices used in the home are always deprived of disposing off[3,5]. They are usually thrown in a dustbin or garbage tank and accidentally comes in contact with the animals which can be the great mediators of infection. The infected needle can also cause harm to the environment as if it gets into any water bodies then the infection will be spread in water. Pharmaceutical industries need to focus on the safe disposal of parenteral devices and have minimum or no contact with the blood flow. To overcome all these problems, the medical field is working on the development of some new devices.

SYRINGE

The word syringe is derived from the Latin word syrinx meaning tube. We all are aware of the syringe as it is mostly used as injecting device. The syringe is a transparent tube that is calibrated and the plunger is fitted inside it which can move inside the tube. Plunger sucks the drugs while moving upwards and pressurizes the drug towards the outside while moving downwards[5]. The common syringe used today is made up of polypropylene and the plunger seal is made from rubber. They are transparent and calibrated by which we can measure the drug to be administered[6]. Syringe is the most used device for parenteral drug administration either by IV, SC, IM, ID. Despite being developed for many years, at present they are having limitations. Some of them are given below:

a) Needle-based injury- The piercing of the needle to health workers is a common limitation of a syringe. According to the WHO report of 2002, 35 million health workers are exposed to infectious disease due to needle-based injury. It has been also mentioned that about 37.6% of hepatitis virus and 4.4% of HIV cases around the world are spread due to needle-based injection.

b) Cross-contamination- The intentional as well as accidental reuse of needles can result in the spread of infectious disease. Diseases like hepatitis B and hepatitis C is having great possibility of infecting a healthy person.

c) Disposal- The correct disposal is always essential for medical devices. Syringe seems a very cheap device for the patient but its disposal is always costly for the government agency. Incorrect disposal of the syringe can put the whole environment in threat[7].

RECENT ADVANCES IN SYRINGE

1. AUTO DISPOSABLE SYRINGE

Many of the government firms are concerned about the reuse of traditional syringes as a matter of spreading disease as well as an economic necessity. The aim of these syringes is to ensure no reuse of

syringes, especially during vaccination. As the name denotes auto disposable syringe is the single use syringe which after on single use is disposed off automatically. These types of syringes have the property of disabling the plunger by locking it after a single use. Auto disposable syringe put us in the advantage of no intentional as well as unintentional reuse of the syringe[8].

The basic mechanism of the auto disposal syringe is that there is a lock at the base of the cylinder in which the plunger gets fitted and finally gets locked after single use. Some of the Auto disposable syringes are also activated before use. The plunger is first rotated clockwise approximately ¼ of total rotation. It is necessary for us to take care of the excess rotation of the plunger, which can misbalance the plunger and air can leak from the side of the plunger. It also provides some other basic advantages like less tiring to use during mass immunization, easy to dispose off as volume to be disposed off is comparatively low, absence of rubber on the plunger which helps in elimination of contamination of drug[9]. Various marketed formulations are summarized in **(Table 1).**

Table 1: Different marketed Auto disposable syringes[9]

Type of AD syringe	**Packaging**	**Require activation**	**Disabled by**	**Fixed needle**
Soloshot	Bulk packaged with plunger caps	No	Metal clip	Yes
Soloshot FX	Individual paper packaging	No	Metal clips	No
K1	Individual paper or plastic package	Remove tab or twist plunger	Plunger break off	Fixed as well as detachable needle available
Destroject	Bulk packed with plunger caps	No	Retches on plunger	Yes
Univec	Individual paper packaging	No	Metal clip and ratchets on plunger	Fixed as well as detachable needle available
Uniject	Prefilled single dose individual package	Push port into needle shield	Reservoir cannot be refilled	yes

The use of these syringes is at a nascent stage in India but the government is advising the health workers to use auto disposable syringes to demotivate the reuse of the syringes. Change in injecting technique is very necessary during the use of AD syringes as the plunger can move back and forward only once so while drawing the drug, they should be careful about no air should be drawn from the

vial[10]. Besides, having the advantage of no reusability of syringe for preventing blood-borne disease, auto disposal syringes have totally failed in preventing needle-based injury. The chances of needle-based injury are more during the activation of syringe.

2. PREFILLED SYRINGE

It is innovative packaging similar to a traditional syringe in which the drug is already filled in the syringe. There is no need of ejecting the drug from the vial. Prefilled as a standalone device and subsystem with other devices has got a lot of attention in recent days. Lack of convenience, affordability, accuracy, sterility, safety, etc. convinced a medical person to move face towards prefilled syringes. Well understood benefits of driving traditional hypodermic needles to prefilled syringes are user convenience, reduced risk of contamination, and reduction of overfill or underfill requirement[11]. They also have the advantage of no reuse of syringe as these cannot be loaded again once the drug is administered in the body. Prefilled syringes are manufactured by nearly 20 pharmaceutical companies mainly for delivering nearly 50 injectables and vaccines[12]. The emerging trends of using prefilled syringe should not surprise the pharmaceutical industries as the advantages of the prefilled syringe are very surprising as they provide safety during loading of the drug as much toxic material from the environment can adhere to the wall of the needle as well as they are very much preferred for limiting needle-based injury while drug loading. With a prefilled syringe, the shelf life of the drug can be increased up to 3 years[13]. The major advantage of the prefilled syringe is, there is no bubble formation in the syringe. Later on Sanofi and rhone Poulenc- Rorer introduced prefilled syringe of heparin. Prefilled syringe got popular in a very short period of time and afterward many therapeutics like anticoagulants, vaccines are manufactured by pharmaceutical companies[14, 15].

ADVANTAGES OF PREFILLED SYRINGES:- There are various advantages of prefilled syringe like they are more sterile as chances of contamination is less due to filling and packing in a sterile environment, filled by hi-tech machine so the chances of overfilling or under-filling of the dose are very low hence provide accurate loading of drug[11], more convenient to use as they don't require the loading of dose[16], more affordable as they don't require the purchase of ampoule and syringe separately and wastage of drug is minimum in case of prefilled syringes as compared to the syringe[14].

DISADVANTAGES OF PREFILLED SYRINGE: - There are various disadvantages of prefilled syringe like prefilled syringes are made up of plastic body and rubber plunger so there are chances of leachability due to direct exposure of drug[17] and some prefilled syringes are made up of type 1 borosilicate glass to prevent leaching but it makes them fragile in nature.

Cyclo olefin polymer and cycloolefin copolymer are the best to replace the glass syringes as they are less leachable, heat resistant, less permeable to water, and are unbreakable[18].

MATERIAL OF CONSTRUCTION OF PREFILLED SYRINGES

Prefilled syringes are mainly made of glass (Borosilicate type 1)[19, 20], and plastic (Cyclo olefin polymer & cyclo olefin copolymer) [21]. It also contains stainless steel, elastomer. The biocompatibility of every material of construction is tested to avoid adverse effects. Biocompatibility tests comprises of

acute and chronic toxicity studies, carcinogenicity, reproductive effect, and irritation of eyes, skin & mucosal membrane. The components of the prefilled syringe are summarized in **(Table2).** An elastic-plastic film tube is attached hermetically to the needle connecting member and the plunger at both ends[14].

Table2: Components of prefilled syringe[14]

Components	Material
Barrel	Plastic/glass
Piston	Elastomer
Tip cap	Elastomer
Plunger rod	Plastic
Needle	Stainless steel
Lock adapter	Plastic
Tamper evident	Plastic
Finger grip extender	Plastic

There are mainly two types of prefilled syringes available in the market. First, in which needle is already attached to it and another one is leur cone syringe in which hypodermic needle is attached by user. The design of both of the syringes differs by the presence of a groove on the neck for the leur lock component. The leur syringe puts the user in the freedom of choosing any size of needle up to convenience[14].

RISK AND CHALLENGES IN THE MANUFACTURING OF PREFILLED SYRINGES:

Prefilled syringes are very challenging as direct nitration of drugs with syringe components can cause serious degradation of the drug. During syringe formation, the tungsten needle is attached to a glass tube by UV-cured glue. The presence of glue between the glass tube and tungsten needle increases the chances of interaction and reaction of the drug. Also, leachable coming out through glue can oxidize the needle and can also give rise to the colonization of aerobic bacteria. This can be controlled by either using a non-cured glue monomer that does not leach out or react with the drug or by alternating the material of construction of the needle. Another challenge faced during the manufacturing of staked prefilled syringes is the use of silicon oil for the lining of the inner tube. Silicon oil is also used as a lubricant for easy passage of the plunger. The prior intention of decreasing the use of silicon oil in the prefilled syringe is a matter of discussion as the interaction of drug and silicon oil is the address of concern. Even medical grade silicon oil can interact with protein and aggregate them as well as silicon oil can be detected as particulate matter during testing. The alternate to silicon oil is the use of silicon emulsion which is sprayed on the inner line of the glass tube and baked at 330 ºC by which water is completely evaporated and the rest of the emulsion gets bind with a glass tube chemically. This process is also known as baked-on siliconization but the disadvantage of baked-on siliconization is

that it cannot be done in an attached-based syringe as this process occurs after boding and adhesive cannot withstand such high temperature and get leaks out from the joint[22].

The challenges of the prefilled syringe are a matter of concern and are continuously minimizing their use significantly. The use of composite polymer in place of glass tubes helps in minimizing the above challenges.

TESTING OF PREFILLED SYRINGES[14]:

Any parenteral preparation should be physically, chemically, and biologically stable for an intended period of time. Likewise, in traditional parenteral dosage form, the prefilled syringe must be sterile and free from pyrogen. As prefilled syringes have both drugs as well as a container so they both need to be regulated under the defined test. Prefilled syringe testing must include the predefined testing and releasing methods for empty as well as filled containers.

a. Testing of empty sterile sub-assemblies: According to Eon, "The impact of drug product on the functionality of syringe cannot be evaluated prior to filling, but testing is needed to confirm the intended purpose for the combination of the drug product." Specific tests are performed to evaluate prefilled syringe like glide force test to evaluate syringe lubrication (ISO011040-4), pull off force testing of the tip cap or needle cap(ISO 11040-4), flange break test resistance testing (ISO 11040-4), Luer cone brake testing (ISO 11040-4), needle penetration test (ISO 11040-4), needle pull out force testing (ISO 11040-4), leur lock collar pull-off force testing(ISO 11040-4), leur lock adapter collar torque resistance (ISO 11040-4), leur lock rigid tip cap unscrewing torque testing(ISO 11040-4). The above tests only provide information on the container only. Final tests are done by assessing the filled containers and closures. Schoenknecht stated, "Performance tests such as breakout and extrusion force measurement should be executed against the user requirement, which should be taken into account the capabilities of the intended patient population".

b. Functionality testing of prefilled syringes: Functionality tests include examination of force required to initiate the movement of the plunger as well as force required to maintain movement of the plunger. These tests are carried out in accordance with ISO standards and GMP guidelines. Schoenknecht says, injection force, break-loose force, and glide force measurement can be challenging because they depend closely on inner diameter of the needle, which can vary within tolerance. Functionality testing of the prefilled syringe is directly affected by the amount of silicon oil used as insufficient silicon oil can cause difficulty in starting movement.

c. Container closure integrity test: Sterility is a foremost attribute for Parenterals. Container closure integrity (CCI) test is performed to ensure the combination product is according to full GMP guidelines and guarantees sterility. CCI test is performed to evaluate the adequacy of container closure to maintain sterility of dosage form. Schoenknecht states, traditional tests such as dye penetration test, leak test, and microbial ingress tests are destructive in

nature and represent statistical results from a small sample of the whole batch. Replacement of these methods was challenging for the researchers. Deter mastic test can be used for evaluating every prefilled syringe. These non-destructive methods include vacuum decay testing, high voltage leak detection, and analysis of headspace within the syringe. An alternative cheap method of destructive test is the helium leakage method. Prefilled syringes can be easily validated by this test. Helium leakage is detected by mass spectroscopy, with ion count proportional to the leak rate[14].

NEEDLE-FREE INJECTION TECHNOLOGY (NFIT)

Despite of being scientific updates on the syringe, there are also such limitations that can prove the use of the syringe very challenging. The invasive mechanism of the syringe is one of the major disadvantages. Many people in the world are needle phobic due to which they are deprived of being vaccinated which results in lower immunity. To overcome these limitations scientists have designed a needle-free injection device which directs the drug parenterally into the skin without piercing the skin. Needle-free injection technology (NFIT) is the technology that uses pressurized compressed gas or spring, which pushes the drug outside through a very narrow nozzle[23]. The pressure of ejecting drug is that much high it can directly cross the skin and get dispersed beneath the skin. NFIT not only reduces the pain at the site of injection but also facilitates us with many advantages like it confines the drug more evenly in the dermis, saves time as well as prevents cross-contamination during mass vaccination.

Typically, NFIT consists of three components including an Injection device, Nozzle, and Air cartridge. Cartridge being capsule-like is filled with carbon dioxide which on activation generates pressure and drives the plunger at very high speed. Nozzle consists of a single hole having a diameter equivalent to the diameter of human hair. NFIT is a scientific gift to people who have needle phobia[24]. They are ideally suited for chronic injections of varying doses of insulin, proteins, and monoclonal antibodies. These are also well suited for solid drug administration directly without using water or any other medium. There are many NFIT based technology in the market like Biojector, vitajet, inject, coolclick, etc but it is expected that dramatic change may occur only when a large pharmaceutical or biotechnology company adopts NFIT and demonstrates its versatility, acceptance, and gain value in the major therapeutic area. Great employment of NFIT can be brought in the army for anesthetics and first aid. Currently, the US army is employing NFIT and it is possible to bring down the startup cost of NFIT if pharmaceutical industries enhance their research so that every country can use it in war[24].

ADVANTAGES OF NFIT: - There are various advantages of prefilled syringe like it provides trouble-free self-administration, saves time and provide increased bioavailability, non-invasive, led to the elimination of reuse of needle and provided more even distribution of the drug in the dermis[25].

DISADVANTAGES OF NFIT: - There are various disadvantages of prefilled syringe like NFIT involves injecting of the drug through pressurizing that's why there are many chances of damaging the fragile molecule beneath the skin[25], and the complexity and cost associated with NFIT are acting as a hindrance in changing and validating the traditional procedure of injecting but despite being high starting up cost, device is cost-effective during use.

Needle-free injection technology works by forcing liquid or solid medication at high speed through a tiny orifice. It basically consists of an air cartridge that forces the piston towards the drug at high speed and creates an ultra jet of drug which penetrates the skin and gets distributed beneath the skin.

TYPES OF NFIT

A. On the basis of drug administered, needle-free injection technology can be classified into three broad categories which are: Powder-based, Liquid injection, and Depot or projectile injection[26]. The design and mechanism of the three injectors are the same but they differ in filling of the drug in the chamber.

1) A powder-based injector is composed of a chamber filled with solid drug powder particles. The drug is stored in the form of cassettes which are capped by the polymeric lid. Activation of the device leads to rupture of helium gas gust which results in movement of powder particle towards nozzle in speed. Pressurized gas pierces the skin. The powder gets impinged with gas stream and crosses stratum corneum and finally got spread beneath the skin. Powder drugs cannot be administrated with a traditional syringe so NFIT is well suitable for administering the solid dosage form. Powder drug administration is mainly painless as a small amount of powder is to be administered which can be administered in a fraction of seconds. Another advantage of the powder dosage form is that it is more stable as well as potent for sustained release of the drug. Powder drug can be coated with gold nanoparticle for gene targeting[23, 24].
2) The principle behind Liquid injection is that if any liquid is having enough pressure and is allowed to force towards outside through a very tiny orifice then it can pinch the skin and get distributed beneath the skin. The design of liquid injection differs from the powder-based injection is that they use gases, spring as well as laser-guided pressure generation mechanisms to drive the piston towards the drug[23, 24].
3) Depot or projectile injection is a highly advanced injecting device used for the delivery of the sustained-release drug. These include the development of a biodegradable depot of spherical size having a diameter of approximately 1mm and should be mechanically strong enough to withstand the high pressure and pierce the skin. Protein antibodies are stuffed in the depot and can be loaded into the device. The device drives the depot beneath the skin. Afterward depot releases the protein antibody in a controlled manner in the body[23, 24].

B. On the basis of driving force, the needle-free injection can be broadly classified into four categories which are; Spring-loaded, Gas driven, Laser guided and Energy propelled.

1) Energy transfer by spring is the simplest way to drive the piston in a pressurized manner. Spring-loaded jet devices mainly contain one or few sets of springs which create pressure in the device. These devices are cheap and are capable of developing enough pressure but they cannot develop pressure strategically as we cannot alter the pressure generated by spring. Another disadvantage of this device is that they start deteriorating with age as spring got fatigued on repeated use[23].
2) No control of pressure in spring-loaded device urges the researcher to develop alters of energy generator which is named as the gas-driven jet device. The gas-driven jet device is the device that uses a cartridge filled with inert gases. On activation, the cartridge releases a strategic amount of gas which generates the required pressure to drive the piston. These are much-used jet devices as we have control over pressure generation[23].
3) The laser-guided jet device seems to be a very advanced jet devices but these are not capable of maintaining the pressure. The design of these devices is very complex and includes the technology of erbium-doped yttrium garnet laser. A laser wave of wavelength 2940nm is emitted when the device is activated. Laser pulse attacks driving liquid generating vapor. The bubble formed forces the membrane leading the drug to forcefully eject from the nozzle[23].
4) Energy-propelled injecting devices mainly work on electricity. The design of energy propelled is based on the technology of the Lorentz force activator which consists of a small and very powerful magnet surrounded by a coil that is attached to the piston present in the drug chamber. When an electric current is applied, the magnetic field is developed which pushes the attached piston forcefully and results in forceful ejection of the drug through the nozzle[27].

RISK AND CHALLENGES OF NFIT

It has been many years of existence of NFIT. Despite accomplishing many advantages, as well as a convincing result during the smallpox epidemic general acceptance of NFIT, is low over the conventional needle. The potential of reaching the medication at the desired site was not up to the strategy of a researcher. Many challenges are faced by the researchers which made NFIT less popular during the early stage[28].

The risk of infection is the foremost concern of a medical person. The very early stage of NFIT is lucky as no cases of infection were reported but in 1990 Hepatitis B infection broke out during large-scale use of NFIT. The risk of infection is mitigated by a scientist named Dimache. Dimache et al proposed a disposal device that got fitted between patient skin and jet injector. The disposable device showed a positive response but replacing this again is another challenge at that time. No use of NFIT on infected sites is the only choice for a medical person in place of a disposable device. It is also practically proven that NFIT cannot be used by a dermatologist as local application of the drug is the foremost choice for them and microbes causing skin disease can make the jet device a carrier. In

addition, leftover drug in drug chamber is another reason of spreading of infection and using of the single-dose disposable cartridge is the simplest solution of this problem.

Pain management is another foremost need of people while using the NFIT device. The invasive method of the needle can cause pain beyond the score of 3. A pain scores less than 3 is always acceptable during the use of any medical device. 1% lidocaine injection administered by NFIT provides immediate analgesia. Zsigmond studied pain management and about 100,000 administered lidocaine injection felt no pain. Many investigators also found NFIT more painful than the traditional needle. Investigator also revealed that pain sensitivity is affected by age, gender, gene, and site of injection. Observing the anatomy of the skin, researcher noticed when injected on the area having thick skin like palm and sole, a person felt very little pain as compared to when the same drug is injected on the contrary site[28]. Injecting of BONT-ONA by NFIT to treat palmer hyperhidrosis is ranked above traditional syringe in pain management. It is hard to compare the result of NFIT and traditional syringe as some scientist believe that facial expression should be a sign of pain in judging pain management while other suggest self-reporting technique of pain. The complex design of jet injector put the person in fear by which facial expression could be changed before administering the drug. It has also been suggested that the use of a spacer, changing driving pressure, changing injection site can be helpful in pain management.

Another emerging risk of using NFIT is maintaining low pressure for injecting ID and SC. Injecting at the superficial layer of skin with a pressurized injecting device termed the use of NFIT very challenging. As we know the driving force of a spring-loaded jet device is approximately 1420 psi whereas gas propelled cartridge can create pressure up to 1800 psi. The pressure of gas propelled jet injector can be changed to maintain the pressure released by the cartridge[31]. Pressure management of traditional spring-based jet devices can be done by using a spacer. Spacer having the size of 1-3 mm can deliver the drug at the desired level as 1mm spacer can push the drug in deeper areas while 3 mm spacer injects the drug in the superficial region. The use of a spacer can also help in mitigating the risk of infection as a spacer can also work as a disposable device that prevents the contact of the device with the skin[18, 19].

CLINICAL APPLICATION OF NFIT

Local anesthesia- 1% lidocaine injection before any minor surgery helps in pain management in needle phobic person. Evenly distribution of anesthesia on the superficial layer of skin results in the potential to decrease the pain significantly. NFIT evenly distributes the anesthesia in the superficial region with systemic effect and can also prevent the damage of inner vessels and nerves. Zsigmond also stated that midazolam and ketamine when injected locally to children show early symptoms of anesthesia by the needle-free jet as compared to any other device except intravenous[32].

Palmar BoNT-ONA- it is very uncomfortable to pierce a needle on palms during treatment of palmar hyperhidrosis (HH) without anesthesia. Needle phobic person always fears getting treatment of HH as the level of pain reaches beyond the score of 3. Treatment of palmer HH needs 60–90minute effect of

anesthesia which is very challenging to get. NFIT can directly inject BoNT-ONA locally with no pain or very little pain. The only disadvantage of NFIT on treating palmer HH is that sometimes drugs get splashback due to which therapeutic concentration cannot be attained[28].

Intralesional corticosteroids- skin diseases like generalized granuloma annulare, nail psoriasis, scars, etc need multiple injections of triamcinolone which could be very challenging by traditional syringes. NFIT can play a vital role in pain management as well as in even distribution of triamcinolone into intradermal lesion for local effect[28].

Intralesional bleomycin use of NFIT in the treatment of periungual warts appeared to be very effective. Keloids and hypertrophic are unresponsive to interlesional corticosteroids while Dermojet injection of bleomycin has proved strategically in treating keloids and hypertrophic scars.

Intralesional 5-ALA (5-aminolevulinic acid) - possibility of vasoconstriction, deep purpura, necrosis, and infection during the process of photodynamic therapy (PDP) urged the researchers to seek the alternative of traditional syringes. NFIT proved to be a very good alternative against traditional syringes. Even distribution of drugs locally expands the diffusion of photosensitizer around the tumors with no pain[30].

Type-2 diabetes mellitus - A new technology needle-free jet injection technology has been developed to replace the insulin pen for increasing subcutaneous absorption of insulin. The researcher studied the effects of insulin glargine injection administered locally in patients with type-2 diabetes mellitus. The study is compared with patients treated with an insulin pen and the results showed that needle-free jet injection of insulin glargine showed increased effectiveness in managing glucose level in patients with type 2 diabetes mellitus as compared to insulin pen[33].

ZyCoV-D - In the Covid-19 pandemic, researchers developed and measured the efficacy and immunogenicity of ZyCoV-D which is a plasmid DNA based vaccine in two doses of 1 and 2 mg using both needle-free injection system and syringe needle intradermally in rhesus macaques. The results showed that the immunogenic response is far better in candidates who received ZyCoV-D using a needle-free injection system as compared to those who received it by syringe needle[34].

Nanopatches

It is another advancement in the needle-free injection system in which drugs are administered into the body of the patient without the use of a needle. It delivers the drug into the dermis and epidermis layer of skin where antigen-presenting cells are present and provide better thermostability and immune response. It contains micro projections which are coated with a vaccine material and move to outer layers of skin containing immune cells by the use of an applicator. It is made by deep reactive ion etching. Nanopatch has also led to a decrease in the amount of adjuvant. The Nanopatch technology was shown using a mouse model in which immunogenicity and efficacy of vaccine increased along with the reduced dose. Some of the vaccines delivered by Nanopatch technology are:

I. Gardasil® - A tetravalent human papilloma virus vaccine.

II. Fluvax® - Seasonal influenza vaccine[35].

CLINICAL TRIALS

This review article is composed of summarized clinical trials related information in the field of needle-free injections in **(Table 3).**

Table 3: Clinical trials based on needle free injections

Title	**Inference**	**Trial phase**	**Status**	**Reference**
Pharmacokinetic and pharmacodynamic profile of insulin lispro using needle-free jet injection technology	Insulin injected using needle free jet technology delivered insulin with high velocity in the subcutaneous tissue and over large area as compared to insulin injected using syringe.	Phase 4	Completed	36
Pharmacology of insulin injected with jet injection in Diabetes	It delivers insulin into the skin with high velocity as compared to insulin pen.	Phase 4	Completed	37
Needle-free jet injection of reduced dose, intradermal, influenza vaccine in >=6 to <24-month-old children	Needle free technology provided reduced dose of inactivated influenza vaccine by intradermal route as compared to two doses by needle-syringe intramuscularly.	Phase 2	Completed	38
Comparison of needle-free injection method with a needle syringe injection method (T-jet®)	Needle free injection method provided better results as compared to syringe method.	Phase 4	Completed	39
Needle-free injection of Lidocaine for Local Anesthesia prior to trigger digit injection (J-tip)	Administration of lidocaine using needle free jet technology provided	Not applicable	Completed	40

	reduction in pain as compared to trigger digit injection.			
JetTouch injection system to deliver saline into the bladder wall of healthy Volunteers	It allowed delivery of saline solution into bladder without the need of needle.	Phase 1	Completed	41
Jet injection for influenza (JIFI)	Seasonal flu vaccine was administered by pharmaJet needle free injection device and results were compared with needle and syringe administration which showed adverse events ratio higher in needle syringe administration.	Phase 4	Completed	42
Pediatric optimization of the PharmaJet needle-free intradermal delivery system (PharmaJet)	PharmaJet technology provided better functionality and performance and is a good approach for delivering injectables into the skin.	-	Completed	43
Phase 1b investigating safety and immunogenicity of TDV given intradermally by needle or needle-free PharmaJet injector	Administration of low dose tetravalent dengue vaccine by pharmaJet showed faster seroconversion as compared to administration by needle syringe.	Phase 1	Completed	44

PATENTS

This review article is composed of summarized patents related information in the field of needle-free injections in **(TABLE 4).**

Table 4: Patents based on needle free injections

Title	Patent no.	Date of patent	Inference	Reference
Safety mechanism to prevent accidental patient injection and methods of same	US 7,887,506 B1	Feb. 15, 2011	A multiuse needle free injecting device was designed to decrease the risk of accidental injections.	45
Needle free injector and process for providing serial injections	US 7,942,845, B2	May. 17, 2011	Needle free injection device was designed to improve the effect of delivery of injectate from device.	46
Needle-less syringe adapter	US 2011/0015566A1	Feb. 10, 2012	The adapter provides filtration of air and prevent the flow of liquid medicine back in the blood vessel of patient.	47
Needle-free injector device with autoloading capability	US 8,172,790 B2	May. 8, 2012	The device consists of actuator which allow auto withdraw of sample from drug reservoir through pressure.	48
Safety syringe for needle-less injector	WO 2012/135943 Al	Oct. 11, 2012	This device prevents reuse of needle by blocking of orifice.	49
Method for making a needle-free jet injection drug delivery device	US 8,591,457 B2	Nov. 26, 2013	It contains method for designing of jet injection device which also provide selection of appropriate pressure range so that penetration up to desired depth can be achieved.	50
Injection device plunger auto-disable	US 8,617,099 B2	Dec. 31, 2013	It designed nozzle for needle free injection device.	51

Improved needle-free injectors	AU 2012205735 B2	Sep. 18, 2014	Making of needle free injection devices with orifice covered with cap to prevent accidental usage.	52
Viscous formulations and their use in needle-free injection	US 9,186,461 B2	Nov. 17, 2015	Needle free injection devices were developed for fast delivery of viscous formulations conveniently and without pain.	53
Needle-less injector and method of fluid delivery	US 9,333,300 B2	May. 10, 2016	A needle less injector was made to provide delivery of specific dose of fluid using high pressure.	54
Vial adapter for needle-free syringe	US 9,345,642 B2	May. 24, 2016	It provided device with combination of syringe and vial which allowed mixing or transfer of constituents.	55
Safety enhanced needle-free injector	WO 2018/080402 Al	May. 03, 2018	It developed needle free injection device with increased safety through porous and non-porous substances.	56
Controlled needle-free transport	US 10 ,326, 347 B2	Jun. 18, 2019	A servo-controlled needle free device was developed which provide high pressure delivery through actuator which can be predicted and controlled.	29

RESULT AND DISCUSSION:

Syringes are the most widely used pharmaceutical aid for the parenteral route. Modification of traditional needles is necessary to make it more advantageous. The disposable syringe came into existence having the aim of automatic inactivation of the syringe after a single use. This is a good modification but not an ideal one as the problem of reusability is solved but needle-based injuries are not declining with its use. Loading of the drug in the syringe is the main reason for needle-based

injury as well it is viable of microbial contamination. Another modification was done and prefilled syringes came into existence in which the drug is already filled in the syringe. Prefilled syringes mitigated the risk of needle-based accidents as well as the risk of disposability is also eliminated. The disadvantage of the prefilled syringe is, it is not able to eliminate the problem of needle phobia. Needle-free injection technology is ideally suited for eliminating the problems associated with the traditional syringe. NFIT can bring a dramatic change in the pharmaceutical field when large companies would accept its versatility and gain wide research acceptance area.

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The author stated that their guardians have given informed consent for publication.

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None

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All authors have the same contribution.

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