"RECENT ADVANCES IN TRANSDERMAL DELIVERY SYSTEM"

A PROJECT WORK (BP812PW) SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

UNDER THE GUIDANCE OF

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MAY, 2022

CERTIFICATE

This is to certify that Project Work (BP812PW) entitled ***"RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEMS"*** *is the bonafide work carried out by* ***BHAVY SHAH (18BPH007), MANREET BUNET (18BPH048), MUDRA VYASA (18BPH052), NRUPA PATEL*** *(18BPH058),* ***PREM PATEL*** *(18BPH68), B.Pharm semester VIII under my guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2021-2022. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

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DECLARATION

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With regards,

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1. ABSTRACT

Transdermal Drug Delivery is an eminent part of the Novel Drug Delivery System, it focuses on delivering drugs directly through the layers of the dermis. It rose to popularity due to a high acceptance rate by not only the Pharmaceutical industry but also by the Cosmetic and Skincare industries. This was due to its painless mechanism of drug delivery and excellent convenience. The appendageal, transcellular, and intercellular pathways are the three primary routes for drug entry. Some elements to consider are skin condition, quality, physicochemical parameters, and environmental conditions. The transdermal drug delivery system (TDDS) allows for medication release to be sustained while also decreasing the strength of action and consequently the side effects associated with oral therapy. Transdermal drugs are doses that are self-contained and distinct. It distributes a medicine into the systemic circulation at a controlled rate through unharmed skin. The epidermis or outer layer in the delivery system regulates the delivery rate. It is tough to create a dynamic complex drug delivery system. It necessitates specific production equipment and processes. This article focuses on different types of Transdermal Dosage Forms – Nano patches, Nano vesicle gel, Needleless injection, and Permeation Enhancing Techniques - Iontophoresis and Microneedles, their mechanism, distinctive features, advantages and disadvantages over conventional dosage forms, currently marketed formulations, recent advancements, and prospects.

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2. INTRODUCTION

Transdermal drug delivery is a perfect way for proper delivery of medications by giving that drug to healthy and suitable skin. So in this process drug enters through the very first layer that is stratum croneum and then into other layers that are epidermis and dermis. A transdermal drug delivery system, commonly known as a transdermal patch or skin patch, is a type of medicine delivery system that delivers a particular amount of medication to the systemic circulation. When therapeutic substances are given through the human skin for systemic effects, physiochemical, biophysical, and morphological aspects of the skin must be considered . Scopolamine transdermal patch was the first transdermal patch authorised by the FDA in 1981. Scopolamine is used to prevent motion sickness and nitroglycerine is used to prevent angina pectoris which is associated with coronary artery disease.

A) ADVANTAGES OF TDDS

TDD provides numerous advantages over other traditional drug delivery methods.

Transdermal system could be like catching substitute to other formulation or methods which can also avoids problems like needle compliance. The huge skin surface and easy accessibility provide for a multiple absorption possibilities. Furthermore it reduces the possibility of side effects. This route is very much suitable for all patients as frequency of dose is also reduced. This system is also suitable for the ones who want to take the drug by its own and also for those who are not feeling well. TDD reduces bioavailability by avoiding pre-systemic metabolism. There are lot many dendritic cells in our skin and that too in both the layes which is dermis and epidermis. So this property plays a pivotal role in immunity which makes transdermal system a best pathway for therapeutic biological molecules. The demand for a low-cost, non-invasive vaccination method, particularly in underdeveloped countries, has prompted extensive study on the invention of simple, needle-free vaccination systems like TDD.

B) DISADVANTAGES OF TDDS

Rashes, local irritation, erythema, and contact dermatitis may be caused by the medication. Lipophilic medications may efficiently pass the stratum corneum, hence the pharmaceuticals must have certain desired physicochemical qualities in order to penetrate. Hydrophillic drugs will not reach the systemic circulation unless they are changed in some way. Because of certain natural limitation of drug entrance imposed by the skin's impermeability, only strong medicines are appropriate candidates for transdermal patch. In a single day, doses of just 5mg or less can be given. The skin's barrier function varies from one location to the next on the same individual, or it could be different for every individual, and with age alsoBecause adhesives may not cling well to all types of skin, the patch may be painful to wear. Transdermal delivery of ionic medicines is not possible.

3. NANO PATCH- TRANSDERMAL DRUG DELIVERY SYSTEM

The nano patches were invented by Professor Mark Kendall from the University of Queensland, Australia. The Nanopatch is a microneedle device that employs microneedles that are tinier and more closely packed than conventional patches, referred as "projections." They are composed of silicon and have 10,000–20,000 projections per sq. cm of 65–120 um in length covered with the vaccine. They will deliver the vaccine via the 'coat and insert' transdermal drug delivery method. They are manufactured to specifically deliver the vaccine at its target site, that is APCs present in the dermal and epidermal region. The main benefit of this device is that it triggers a specific and enhanced immunological response, which has been demonstrated in a small animal model. Potential advantages include painless administration and thermostability and minimal chance of needle-stick injury. Using commercially available influenza vaccine antigen, inactivated whole chikungunya virus vaccine, and DNA-delivered inactivated West Nile virus vaccine, NP immunization has been shown to be effective.

Nanoparticles could improve macromolecular medication penetration across the stratum corneum, potentially lowering immunogenicity and increasing bioavailability. Self-assembled liposomes, solid-lipid nanoparticles (SLNs), polymeric micelles, and inorganic nanoparticles are the most frequent nanoparticles employed for transdermal drug administration. Inorganic nanoparticles, such as gold, silica, and iron oxide nanoparticles, have superior chemical and mechanical stability than organic nanoparticles, are easier to surface functionalize, and have a variable particle size and morphology. As a result, one of the fastest expanding disciplines in nanomedicine is the development of innovative transdermal nanodevices based on inorganic nanoparticles.

As the microneedles are known to be a painless approach to drug delivery due to their low reach in the nervous tissues, they were combined together in form of a patch, known as a Nano-patch. By merging microneedles with a patch-like structure, a device with all of the benefits of a typical transdermal patch, such as continuous release, the convenience of use, unobtrusiveness, and painlessness, may be created. A microneedle-based patch, unlike a normal patch, can deliver nearly any macromolecular substance (including insulin and vaccine). Not only would such a patch provide an unobtrusive and patient-friendly drug delivery system, but it would also be an efficient and possibly safe means to administer drugs with limited intervention from healthcare experts.

Nanopatch focused distribution of both antigen and adjuvant (QuilA) to the dermis allows for unprecedented dose reductions of up to 900 times with vaccination compared to intramuscular injection. Coating and nanopatch technology has been extensively tested in mouse models using different types of vaccines (human papillomavirus, herpesvirus type 2 (HSV2) DNA vaccine, chikungunya fever, West Nile virus, etc.)-each study is nanopatching. Has been shown to improve immunogenicity compared to needles and vaccines.

A) MECHANISM

The Nanopatch method consists of a large number of vaccine-coated microneedles that break open into the upper layers of the skin when delivered with an applicator device. The vaccine material is coated on the points of Nanopatch's microprojections allowing it to reach a large number of critical immune cells just beneath the surface of the skin. Deep reactive ion etching is used to make the nanopatch. The Nanopatch array is at the heart of this technology, consisting of a 1 cm2 silicon square with comprising 20,000 invisible microprojections on its surface. Using microprojections with optimised spacing and length, The Nanopatch matrix bypasses stratum corneum to deliver completely resistant material to the immune-cell-rich layers just underneath it. The outcome, as revealed in a mouse model, is an effective increase in immunogenicity that can be employed for two motives: minimizing the dose necessary to attain efficacy, (a 100-times decrease was obtained in the mouse model while delivering Fluvax®) or enhancing vaccination efficacy. Preclinical tests have also demonstrated that the Nanopatch can eliminate or drastically lower the amount of adjuvant needed for effective vaccination.

Formulation and coating

Microprojection needles must be produced to the precise shape, and also uniformly covered to assure that the Nanopatch device supplies a substantial of vaccine to the required targets. A vaccine-containing formulation is applied to the produced patches. Coating processes have been refined to be adaptable and apply coating compositions quickly and efficiently with high efficiency. The coatings are strong and stable at room temperature, thus, they stay preserved when implanted by the epidermal layer and release rapidly (typically seconds) when they come in touch with the hydrated dermis.

Applicator

The qualities of the epidermis vary greatly based on age, gender, health, and even humidity levels in the environment. This introduces uncertainty, which must be overcome if vaccine distribution is to be consistent and reproducible. The Nanopatch method accomplishes this by conjoining covered Nanopatch arrays with a thoughtful applicator. It compensates for skin variances by utilising our understanding of the dermis's mechanical characteristics to enable uniform distribution and penetration throughout a patient population's natural diversity. Other transdermal vaccination administration systems suffer from inconsistency due to the applicator design.

B) MARKET FORMULATIONS

A variety of vaccinations have been delivered using Nanopatch technology, including

• inactivated whole virus vaccines (e.g., FluVax® – commercially available seasonal influenza vaccine),

• virus-like particles (e.g., Gardasil® – commercially available tetravalent human papilloma virus vaccine),

• DNA plasmids (e.g., preclinical herpes simplex virus 2 vaccine) and other compositions have all been delivered using the Nanopatch technology.

These dry-coated Nanopatch vaccines have long-term thermostability, with efficacy comparable to newly coated devices or those coated and stored at 23oC for over 6 months before applying them on theskin.

C) ADVANTAGES OVER CONVENTIONAL DOSAGE FORMS

The fundamental characteristics of Nanopatch delivery technology give several major advantages, including:

Improved immunogenicity

By delivering the vaccine directly to critical immune cells, the Nanopatch can either amplify the immune response induced by a vaccine or allow for the formation of an adequate immunological response with a portion of a full vaccine dose. Indeed, preclinical tests have demonstrated that the Nanopatch can provide a preventive immunostimulatory reaction with a fraction of the amount of syringe needle necessary.

No cold chain Required

The vaccine can be kept stable at room temperature because of the coating compositions being used to coat the patches. As an outcome, vaccine distribution would no longer be dependent on the expensive cold distribution chain that is currently required to prevent temperature degradation, which can render traditional vaccinations ineffective or potentially hazardous. Temperature stability also opens up the possibility of providing vaccinations in areas where cold chain infrastructure is unstable or non-existent.

Needle free

Nanopatch microprojections require the use of an applicator to pierce the skin's protective outer layer and deliver a vaccination. This is in contrast to the conventional syringe needle, where needle stick injuries are prevalent and can have catastrophic repercussions owing to infectious disease transmission. Because the Nanopatch projections are not visible to the eye normally, they are unlikely to cause distress to persons who loathe needles; this is predicted to enhance compliance.

Pain free

The Nanopatch's microprojection array is designed to deliver vaccine directly to specific immune cells just beneath the skin's surface. The Nanopatch delivery system is expected to be painless because these extensions do not reach a layer where they hit nerve endings.

Cost effective

The Nanopatch vaccine delivery system is designed and developed using well-established manufacturing techniques in order to achieve high volume, low cost manufacturing. There may be additional cost savings as a result of some of the other benefits described above, such as using less vaccine to achieve successful immunisation, eliminating cold chain costs, and a significant reduction in the expenses involved with needle stick injuries.

We believe that this platform technology will be suited for delivering the vast majority of vaccines due to its strong and unique features.

D) DISADVANTAGES

In actuality, because it is both unrealistic and erroneous, a one-size-fits-all strategy to assessing the potential hazards and advantages of nanotechnology for public health is not viable. Nanostructures come in a variety of shapes and sizes, and not all of them are safe. Many factors should be considered when evaluating the potential risks associated with a constructed nanomaterials: the likelihood of being exposed to nanomaterials that may be lost by the them; whether there are any hubs of health hazards to shed nanoparticles throughout the nanomaterial's life span; identifying who and what could be exposed; and the eventual fathoming of the risks.

The intrinsic hazard attributes of compounds incorporated in nanoparticles, as well as particle size, shape, surface charge, and physicochemical properties, are particularly important, as these all regulate cellular uptake and the possibility of future health impacts. To summarise, nanoparticles are more dangerous than bulk material if they are

insoluble, breach biological membranes, remain in the body, or are elongated and fibrous (in the case of inhalation exposure). Nanomaterial development should ideally embrace a safety-by-design strategy, as nano-enabled products with lower possible effects on health and wellbeing have a commercial advantage.

4. NANOVESICLES SYSTEMS FOR TRANSDERMAL DELIVERY SYSTEMS

Nanovesicles are promising and adaptable delivery and targeting methods for medicines, biomolecules, and contrast agents. Even though the first research in this field used phospholipid vesicles, there is growing interest in the use of alternative compounds to create smart vesicular carriers that focus on tailored delivery tactics.

Nanovesicles constitute one of the most promising and successful techniques for developing medicines for cancer, infection, and degenerative diseases.

Transdermal medication administration has long been one of the most popular drug delivery methods.

In the last decade, Transdermal delivery methods are classified as first-formation, second-formation, or third-formation. Ultrasound, chemical boosters, and iontophoresis, which do not rely on cavitation, are used in first-formation delivery systems for small-sized, low-dose medications, and lipophilic whereas chemical boosters, ultrasound, and iontophoresis are used in second-formation delivery systems for small-sized, low-dose pharmaceuticals, and lipophilic. Microneedles, microdermabrasion, electroporation, thermal ablation, and cavitation ultrasound are all used in third-formation delivery systems to target the stratum corneum.

We detailed the contemporary lipid-based Nano vesicular systems, whether biological or synthetic in origin, that are employed for a variety of biomedical and therapeutic applications in this study.

Nanovesicles such as niosomes, proniosomes, ethosomes, transferosomes, and phytosomes are being studied for drug delivery applications.

To improve the transdermal distribution of a hydrophilic model molecule, it combines lipid nanovesicles (ethosomes, liposomes) as drug carrier systems with two physical approaches (electroporation and sonoporation).

A) RECENT ADVANCES IN NANOVESICLES FOR TDDS

Nanovesicles are spherical bilayer vesicles invented of lipids or analogs like surfactants that are nanoscale in size. Niosomes, Proniosomes, transfersomes, ethosomes, and phytosomes are some of the nanovesicles utilized to ease transdermal distribution. The principal component employed in the formulation is used to classify these nanovesicles.

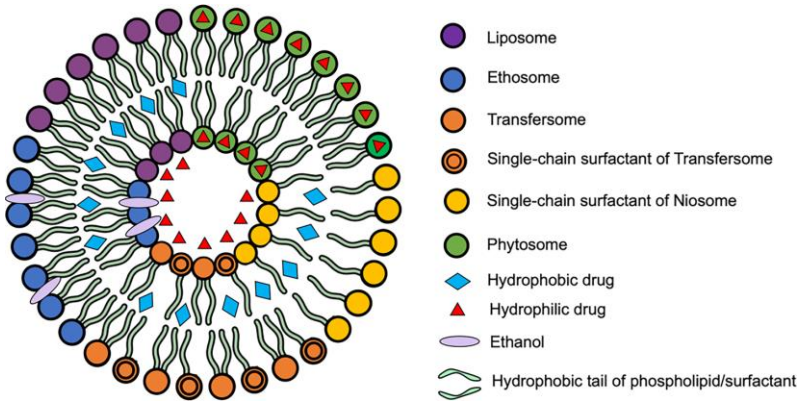


Figure 1

1) Niosomes and Proniosomes:

Niosomes and proniosomes are Lipid Nano vesicular systems with unique amphiphilic features that can increase the bioavailability of poorly soluble medicines. Their nonionic surfactant backbone distinguishes them from other vesicles, and their multilamellar and unilamellar vesicles resemble liposomes in structure.

Proniosomes are powdered or gel-like nonionic dehydrated structured provesicles. Provesicles are water-soluble, dry, free-flowing granular commodities that may be rehydrated just before use, avoiding many of the issues associated with aqueous vesicular dispersions.

Cholesterol, non-ionic surfactants like Tween 20, 40, 80 and Span 20, 40, 60, 80, 85 solvents such as chloroform and methyl and ethyl alcohols, and lecithin may all be used to make proniosomes and niosomes. Surfactants used to make niosomes and proniosomes typically have limited water solubility, however, Tween can be effectively employed to make micelles after hydration. Cholesterol, Tween 80, Sorbitol, and Sucrose are all found in proniosomes such as Letrozole, which is used as a topical breast cancer treatment. Naproxen is an anti-inflammatory drug that includes cholesterol, lecithin, and Span 60. Niosomes, such as Tamoxifen citrate and doxorubicin, include Cholesterol and Span 20 and are used to treat topical breast cancer.

Figure 2 STRUCTURE OF PRONIOSOMES LIPID NANO VESICULAR SYSTEM

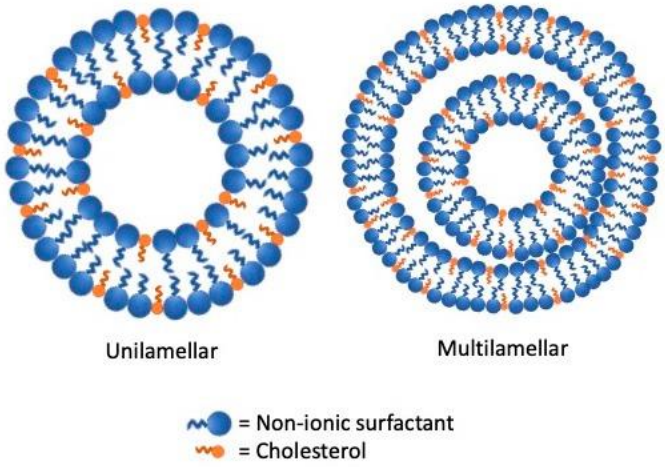


Figure 3 STRUCTURE OF NIOSOME LIPID NANO VESICULAR SYSTEM

2) Ethosomes:

Ethosomes are non-invasive passive lipid-based delivery devices that have been invented and developed. It denotes those carriers are lipid bilayers made up of

phospholipids, water, and high ethanol concentrations and that they have exceptional transdermal permeability. In the polar head group area, ethanol and lipid molecules increase membrane fluidity and permeability.

In both occlusive and non-occlusive circumstances, ethosomes greatly increased skin delivery by transporting drugs into deep layers of the skin. They have great stability, encapsulation efficiency, deformability, and a negative charge owing to the ethanol, which results in tiny vesicles and good bioavailability. Despite these benefits, the volatile nature of ethanol has several drawbacks, including issues with system medication leakage and skin irritation. Antifungals, antivirals, and anti-inflammatories have all been effectively administered through these vesicles. Cholesterol and lecithin are found in hyaluronic acid, which is used to transport medicines transdermally. Transdermal vaccination administration of HRP IgG includes Soy phosphatidylcholine and cholesterol.

Figure 4 STRUCTURE OF ETHOSOMES LIPID NANO VESICULAR SYSTEM

3) ***Transferosomes:***

Many drug delivery methods have been developed for transdermal administration in recent decades, which has several advantages over conventional routes, including the potential to avoid presystemic metabolism, optimize drug release, reduce drug level variance, and improve pharmacological response. Lipid

vesicles, unlike most other transdermal delivery systems such as sonophoresis, chemical permeation enhancers, and microneedles, may transport both lipophilic and hydrophilic medicines due to their distinctive makeup.

Transfersomes are ultra-deformable elastic vesicles that have been effectively used as a non-occluded technique of permeating skin via the stratum corneum and reaching blood circulation and the dermis. They are initially distinguished by an aqueous core surrounded by an amphipathic lipid bilayer of phosphatidylcholine, lecithin, or a combination of lipids.

They include 10–25 percent bilayer-softening complexes, surfactants, or edge activators such as Spans, sodium cholates, Tweens, and deoxycholate, in addition to a modest quantity of alcohol (3–10 percent).

Transfersomes are phospholipid- and edge-activator-based ultra-deformable liposomes. In comparison to typical liposomes, the edge activator destabilizes the lipid bilayer, making transfersomes significantly more flexible and bendable.

Tamoxifen is a transdermal medication for breast cancer that comprises soy phosphatidylcholine and emu oil. Soy lecithin and sodium deoxycholate are found in HGH, and it is delivered through the skin.

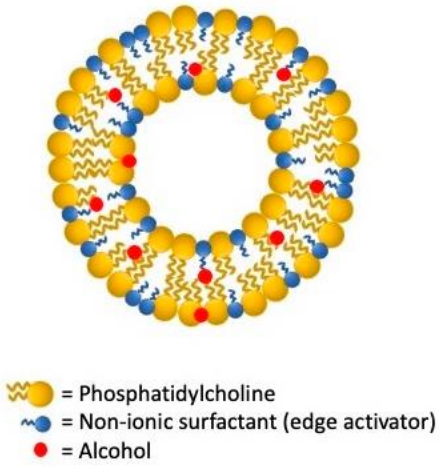


Figure 5 STRUCTURE OF TRANSFEROSOMES LIPID NANO VESICULAR SYSTEM

4) Phytosomes:

Phytosomes, which are lipid-based nanovesicles made up to promote the distribution of hydrophilic phytoconstituents, were created for improving medicine absorption via the skin. Because active elements from phospholipids and plant extracts are complexed by covalent connections, they are also known as phyto-phospholipid complexes.

Thus, unlike liposomes and other equivalents like ethosomes or transfersomes, drug molecules are entangled in phytosomes. The hydrophilic drug is entangled as a compound in the polar head of the phospholipid in phytosomes, whereas the drug is enclosed in the interior of the vesicles in liposomes.

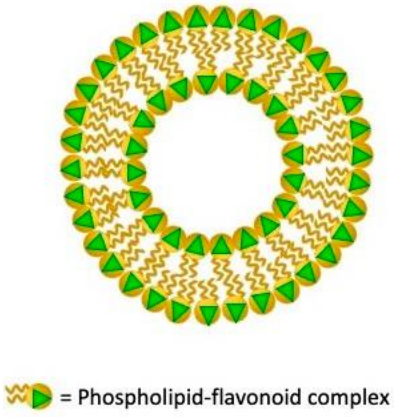


Figure 6 STRUCTURE OF PHYTOSOMES LIPID NANO VESICULAR SYSTEM

S. No.	Additives	Liposomes	Ethosomes	Transethosomes	Examples	Uses
1.	Phospholipid	Present	Present	Present	Soya phosphatidyl choline	Vesicle forming component
2.	Polyglycol	Absent	Present	Present	Propylene glycol	Skin penetration enhancer
3.	Alcohol	Absent	Present	Present	Ethanol	Softness for vesicle membrane
4	Cholesterol	Present	Present	Present	cholesterol	Stability provider to vesicle membrane
5.	Vehicle	Present	Present	Present	Carbopol D934	Gel former
6.	Surfactant	Absent	Absent	Present	Sodium cholate	Edge activator

Table 1 COMPOSITION OF LIPID NANOVESICLES SYSTEM

B) ***MECHANISM OF NANOVESICLE GEL IN TDDS***

The four possible modes of action of lipid nanovesicles as medication delivery systems for the transdermal.

a) The penetration enhancing mechanism;

b) Vesicle adsorption to and/or fusion with the stratum corneum;

c) Intact vesicular penetration mechanism (intact vesicles penetration into intact skin);

d) Trans-appendageal penetration.

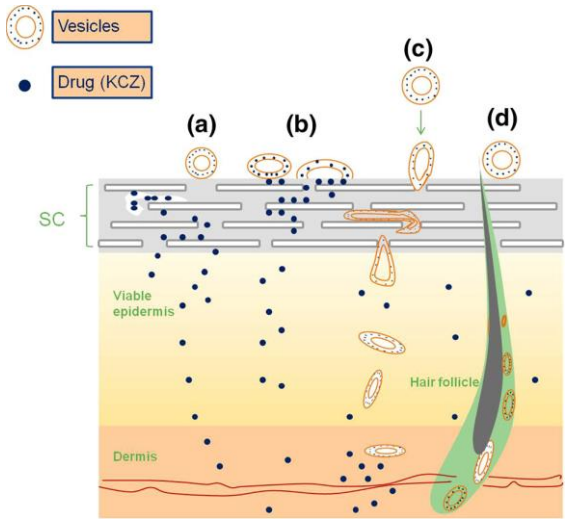


Figure 7

Alternative methods for innovative liposomes working as transdermal medication delivery systems have been proposed in recent decades of research. To begin, the penetration-enhancing process modifies the liposomal as phospholipid bilayer and interacts with skin lipids, resulting in increased fluidity but a lower skin lipid phase transition temperature.

Secondly, vesicle adsorption to and/or fusion with the Subcutaneous corneum, in which the vesicles may adsorb to the Subcutaneous corneum surface, allowing medication to be transferred directly from the vesicles to the skin, or vesicles may fuse and mix with the Subcutaneous corneum lipid matrix.

Thirdly, intact vesicular skin penetration mechanism, i.e., great deformability of these vesicles as a result of the edge activator, leads to intact vesicular skin penetration and deep penetration.

Last but not least, there was a trans appendageal invasion. However, it has been proven that vesicle penetration into but not surely via hair follicles plays no significant part in vesicle skin delivery.

C) DEFORMABLE NANOVESICLES SYNTHESIZED THROUGH AN ADAPTABLE MICROFLUIDIC FOR ENHANCED LOCALIZED TDDS

Phospholipid-based deformable nanovesicles (DNVs) with shape pilability provide a versatile and simple way to encapsulate a wide range of medicines and enable targeted transdermal administration while limiting systemic exposure.

Scientists characterized, synthesized, and evaluated DNVs containing the fluorescently tagged hydrophilic bisphosphonate medication AF-647 zoledronate to see if they could be administered transdermally to a local location (AF647-Zol). DNVs from the AF647-Zol strain were resuspended, lyophilized, and administered transdermally to the calvarial skin of mice as a mixture.

Hand-mixing and postprocessing comprising extrusion, sonication, and freeze-thawing are common in traditional NV and DNV manufacturing procedures. A microfluidic-based NV manufacturing process might be a powerful solution to these technological difficulties. Deformable vesicles created later, such as ethosomes that contain liposomes with a high ethanol content have shown promise in topical administration, mainly for lipophilic drugs.

The lack of consistency in vesicle size and drug entrapment effectiveness in traditional synthesis methods has severely hampered the clinical development of NVs and DNVs.

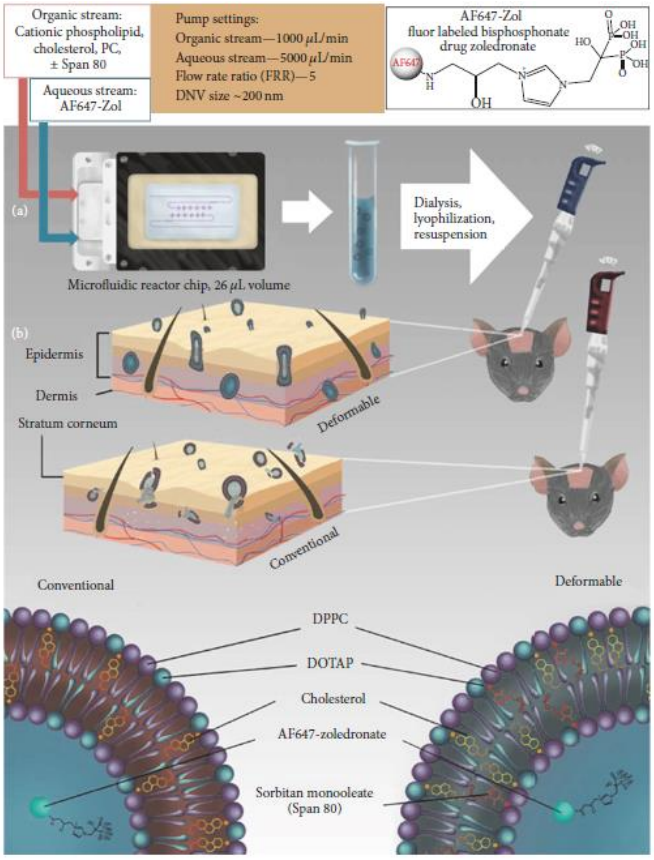


Figure 8 Synthesis and testing of drug-loaded conventional and deformable NVs.

Above showing the image, Synthesis was carried out in a 26-liter microfluidic chamber, where controlled and confined laminar diffusive mixing of aqueous AF647-Zol solution and lipid membrane components dissolved in isopropyl alcohol occurs within the microchannels, resulting in the formation of homogeneous, repeatable populations of drug-loaded NVs, which can be deformed with the addition of the edge activator sorbitan mono that is span 80. Before being applied to shaved calvarial skin of wild-type C57Bl6J mice, the drug-loaded NVs and DNVs were lyophilized, diazed, and resuspended. A free AF647-Zol aqueous solution was also employed. Deformable NVs enter the outer dermis more easily through the nanopore without rupturing and letting out cargo before reaching the target.

D) NANOVESICLES APPROACH FOR TARGETING FOR MECHANISM OF ANTIPSORIATIC

Psoriasis is a severe autoimmune disease characterized by abnormally developing keratinocytes that alter the skin's barrier function, making topical medications ineffective.
The nanovesicular method is most successful for providing regulated freely and therapeutic control at the appropriate spot.

For centuries, vesicular delivery carriers such as first-formation vesicular structures such as liposomes and their modified forms have been used for effective transdermal administration of a variety of medicines, but this is still an area where innovation is needed.

Nanovesicles also offer several benefits, including significant penetration into the stratum corneum, biocompatibility, simplicity of manufacture, stability, and inertness. As a result, the Triamcinolone acetonide-loaded transfersomes have been designed and optimized for the delivery of corticosteroids in the current study. Different ex vivo and in vitro characterization criteria were performed on the nanovesicles, and the best carriers were then integrated into a gel as the concluding formulation.

In the psoriatic animal model, the total inquiry reveals that the newly created formulation can effectively target the steroid-mediated mechanism of antipsoriatic treatments for successful skin condition management.

E) OVESICLE FOR TRANSDERMAL DELIVERY OF FELODIPINE

It traces the development of nanovesicles to attain enhanced topical delivery of felodipine and also investigates parameters for optimization of variable membrane compositions that include soya- and egg lecithin and edge activator.

Transfersomes as a highly effective transdermal carrier for the passive transport of felodipine, which is lipophilic but partially insoluble in water. The study also shows how the edge activators affect, the kind of lipid the morphological and functional characteristics of transfersomes. The span and soya lecithin combination had the best outcomes and transported the most medicine over the skin.

In vivo pharmacokinetic studies and confocal laser scanning, microscopic studies found that felodipine-loaded transfersomes permeated rapidly into the bloodstream, resulting in high drug plasma levels and improved ability of absorbed substances. The study found that transfersomes penetrated the skin quickly and noninvasively, allowing for fast therapeutic drug levels in plasma at lower doses while avoiding felodipine's hepatic first-pass metabolism.

F) CHALLENGES AND FUTURE PERSPECTIVES OF THIS APPROACH

Liposomes have been explored extensively as drug delivery nanovesicles due to their potential to carry bioactive compounds of various sizes and to target specific cells/tissues via chemical alterations to their surfaces. Surface chemical changes, on the other hand, are not necessary to make targeted exosomes since they already have this ability due to

cellular and lipid adhesion molecules expressed on their surface. However, difficulties loading large bioactive compounds into exosomes have necessitated the creation of a unique hybrid system based on liposome-exosome membrane fusion.

Liposomes continued to pose several obstacles. Liposomes are without a doubt the most effective family of nanomedicine. However, despite 60 years of study, only a few liposomal medicine formulations have reached the market, indicating that the full potential of liposomes has yet to be realized. Liposomes' possible harmful effects, leakage, stability issues, batch to batch repeatability, efficient sterilizing procedures, and scale-up issues are the key reasons for their poor transfer rate from bench to bedside.

5. MICRONEEDLES: TRANSDERMAL DRUG DELIVERY SYSTEM

Microneedles are mostly solid and hollow cannules with exterior diameter upto 290 millimetres and length of almost 100 to 1000 millimetres. For transdermal drug delivery, microneedles can be manufactured within a patch. Patches with microneedles have been tested for a variety of applications, including pharmaceutical, biopharmaceutical and vaccine administration. The disturbance of the stratum corneum by microneedles causes a significant response. Microneedles were actually proposed in the year 1976, but the technique with actual micro diameter did not become industrially accessible until the year 2001. Needles which are made up of silicon, metals and other materials have been produced using the microelectronics industry’s low-cast mass-production equipment. Microneedles were developed to pierce the upper layer of skin up to a depth of 60 to 210m. Because microneedles are miniature, they do not reach at inner layer that is dermis nerves which allows for effortless application. When compared to other transdermal administration systems, microneedles are more efficient of boosting drug movement all over the skin. Microneedling is a newer less invasive procedure that includes rolling micro thin needles across the skin to puncture it softly and controllably. It has gained widespread recognition and acceptability in a short amount of time since it is a simple, inexpensive, safe, and effective approach that requires little training. It was originally

employed as a collagen induction therapy for face scars and skin rejuvenation and is now commonly utilized as a transdermal delivery system for therapeutics medications and vaccinations.

A) ADVANTAGES

The advantage of microneedles has rapidly grown with the advancement of basic industrialized techniques and the insight accumulation. Microneedles outperform conventional needles in terms of convinence, safeness, extraction osf any sample and many more. At the same time, many different microneedles have launched, each and every with its own applications and advantages. When compared to standard hypodermic needles, the minimum degree of invasiveness is the most potent advantage of microneedles. When needle length and width are measured in microns, the skin damage occurred by every needle is minimal. This has many other advantages:time of recovery is much faster, microbiological creatures are very less likely to enter body through the holes of needles and bleeding problem is also reduced. In terms of production, the MNs technique is more cost effective. Mns are highly stable as previously, because they require drying phase after production, leading in stable increase. Basically this eliminates the cold chain storage need and some transportation scheme, which has significant hit in underdeveloped countries where many facilities are limited. In addition, in developing countries, the reuse of hypodermic needles is a persistent problem. Most MNs are dispensable drug products without any biohazardous loss, and also low pollution. Pain, infection, and damage are all reduced when microneedles are used. Microneedles allow medications to enter the systemic circulation quickly. The gastrointestinal tract is bypassed when medications are administered using microneedles. Microneedles can transport tiny chemicals, macromolecules, vaccinations, or nucleic acids to the living epidermis in a regulated manner. Unlike traditional immunisation, which uses a high vaccine dose, microneedle patch delivery uses a much lower amount of vaccine to target the skin's rich immune system, resulting in a stronger immune response and more effective use of the antigen. Because of their small active area, microneedle delivery methods are expected to require such increased reactions in the future.

B) DISADVANTAGES

Microneedles have the following drawbacks: If there is a plenty amount of drug under the skin, it can cause local irritation. Allergies and sensitive skin can cause skin irritation. Microneedles are difficult to put to the skin, and the practitioner must learn how to do so properly. Because the needles are so little and considerably thinner than hair, the microneedle tips can be snapped off and buried beneath the skin. Accuracy of dose is almost lower than that of hypodermic needles. Very careful use of device is must which can avoid the bouncing of the surface of skin. As if the device is not held straight up, the dose will break or skin penetration will occur up to varying degrees. Thickness of the upper layer that is stratum corneum and all the other layers varies among every individual so particle insertion depth also varies. The exterior environment such as skin moisture may have an impact on delivery. The microneedle point may crack and persist beneath skin when this patch is removed, causing vein collapse.

C) MECHANISM OF DRUG DELIVERY

The drug substance is delivered mostly through transdermal route using different mechanisms of diffusion. The skin is briefly disturbed in the microneedle medication delivery device. A microneedle device is manufactured by aligning more than hundreds of microneedles array or tiny patch which is similar to industrially available patch to administer efficient medication to provide desired response. The barrier layer is bypassed because it breaks the layer that is stratum corneum. The medicine is injected into epidermis and dermis layer directly after which it can enter directly into blood and produce immune response when it reaches the actual location.

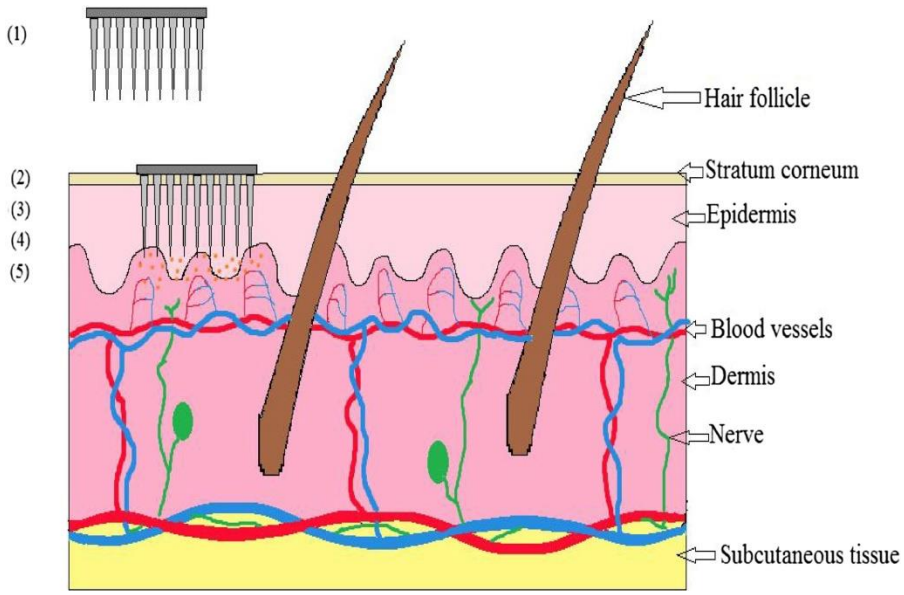


Figure 9

D) TYPES OF MICRONEEDLES

Inspite the different designing of the microneedle which is based upon administration technique, different microneedle form and medication action which is to be delivered, most of the patches share many similar characteristics. A typical microneedle has a tapered sharp tip and measures 150–1500 m in length, 50–250 m in breadth, and 1–25 μ in tip thickness. A wide range of metals, different glass material, ceramic etc are the most common materials used to make microneedles. In most cases, the drug is deposited mostly inside the microneedle or on the surface of microneedle which is then affixed to substrate surface beneath together make array. For convenience of usage, the microneedle is bonded to back side of patch, which comprises skin adhesive for promoting skin interaction. Microneedles are usually divided into four categories: Solid microneedles are composed mainly metal and silicon, which have good mechanical qualities and don't contain any medications. When these coated microneedles are enforced into the surface of the skin the drug delivery will occur exactly at the same time of application. The medicine can be contained in the biodegradable matrix when dissolving microneedles, resulting in no sharp waste following microneedle application. Since the drug is present

in all the areas of microneedle, hydrogel microneedles allow for delayed drug delivery. Because microneedle characteristics vary by kind, a suitable design for the microneedles should be chosen based on the medication dose , action point, time for delivery, distribution, packing, bio waste and time considerstion to wear that patch.

SOLID MICRONEEDLES

This is typically used by forming pores to prepare the skin for the process or treatment. The needles sharp tips pierce the skin surface, creating micron-sized holes via which the medicine enters the skin layers directly when a drug patch is applied. The Poking and Patching technique incorporates the skin perforation with solid MNs to create microchannels that reach the epidermis' innermost layers. Because the stratum corneum, the skin's principal barrier to permeability, is disturbed, this approach dramatically enhances passive drug transport through the skin. This method consists of two steps: First, the MNs pierce the epidermis and are then removed; second, the medicine is given in a traditional dose form (solution, cream, or patch), which acts as an external drug reservoir. The fabrication of microneedles with height of 150m and a width of 105m were successful. They also created different solid silicon microneedle which is coated with gold which ha height of 230m, width of around 50m, a tip angle of 20 and 40m diameter. Bioavailability and strength were both improved as a result of research. Scientist investigated microneedles made up of polylactic acid and discovered that these biodegradables have enough mechanical strength to puncture the upper layer and also improve the absorption of drug. But problem occurred was micro pores open only for a very short period of time which can block the transport of active substance.

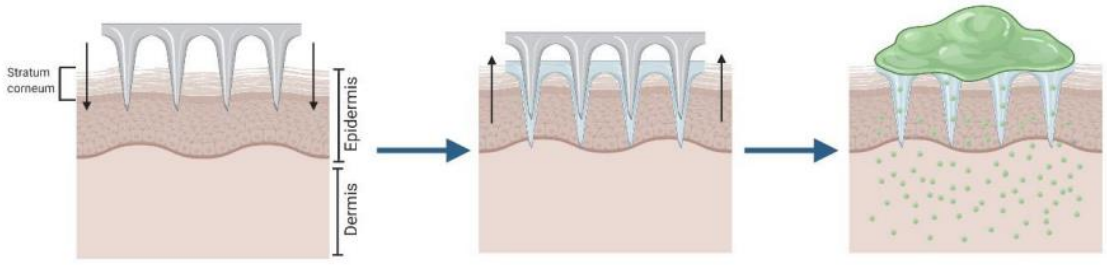


Figure 10

COATED MICRONEEDLES

The drug solution or drug dispersion layer surrounds the microneedles. The Coating and Poking technique, involves coating of the solid microneedles surface with a medication or vaccine-loaded formulation, is another approach utilizing solid MNs. After MNs implant, this approach allows drug diffusion to the deeper layers of the skin from the surface which is coated. The applicability of this method is limited by a number of challenges, most of which are connected to the coating. The quantity of drug that can be enclosed in the coating layer, for example, is somewhat limited. Furthermore, the thickness of the coating might reduce the sharpness of the microneedles and affect their capacity to perforate the skin. The use of a coated microneedle to deliver various drugs through the same formulation was also investigated. Scientist coated individual microneedle with distinct methods and drug substances, allowing numerous agents with varying characteristics to be delivered simultaneously. These effectively supplied both water soluble and water insoluble dyes.

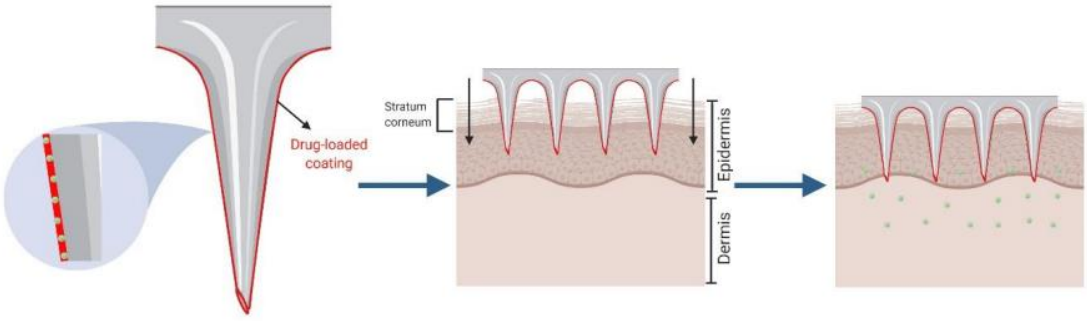


Figure 11

DISSOLVING MICRONEEDLES

These types of microneedles are made with the help of biodegradable polymers and also the drug is filled within polymer. Dissolution occurs when the microneedle is inserted in skin surface, releasing the drug substance. As the microneedle is not properly taken after insertion, this process includes only one step. After all this polymer gets degrade and allows the release of medication. These needles have very good patient compliance. It is

also the best option for therpy based for long time as it has very good bio acceptance of the polymer and also the dissolution which takes inside skin. Some scientist created microneedles with tin that deliveres drug quickly and effectively without causing any skin problem. This needle takes very long time to get dissolved. Therefore complete insertion is very difficult.

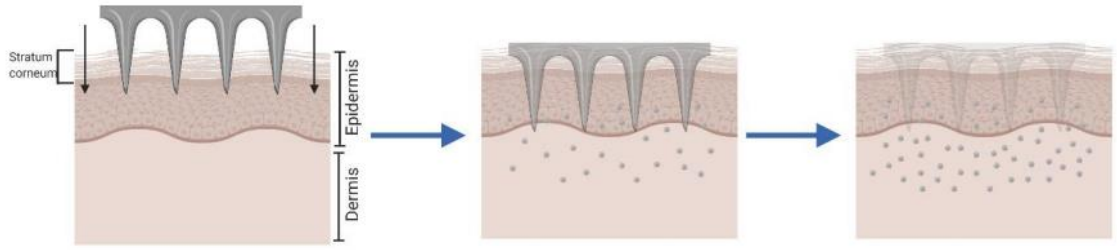


Figure 12

HOLLOW MICRONEEDLES

Hollow MNs are a type of microsyringe with needle length and diameter decreased to the micron level. With a perforation in the needle tip, there is an empty area inside the MN to retain the drug dispersion or solution. The Poking and Flowing method was devised to deliver a drug into the surface of skin in a manner that resembled hypodermic injections while eliminating its drawbacks. Microneedles are used in this method in a similar way as hypodermic needles, which are used to inject medication formulations following skin perforation. Their manufacturing process is complicated and expensive because they have very small that is micro size which requires high techno resources. And on other hand patient is very comfortable with this procedure than that of regular injections, thanks to the smaller size of these needles. Since more drug substance can be accommodated in the empty area inside the needle, these microneedles can deliver a big dose of medication. It's crucial to keep the flow rate steady in this situation. Using hydrofluoric acid etching, Maaden and colleagues created fused silica hollow microneedles. So this microneedle gives very less amount of vaccination to the skin surface by its own which can avoid the drawback of hypodermic needle. Also few scientists constructed this needles that mimicked mosquito action. And they were found to have better skin penetration.

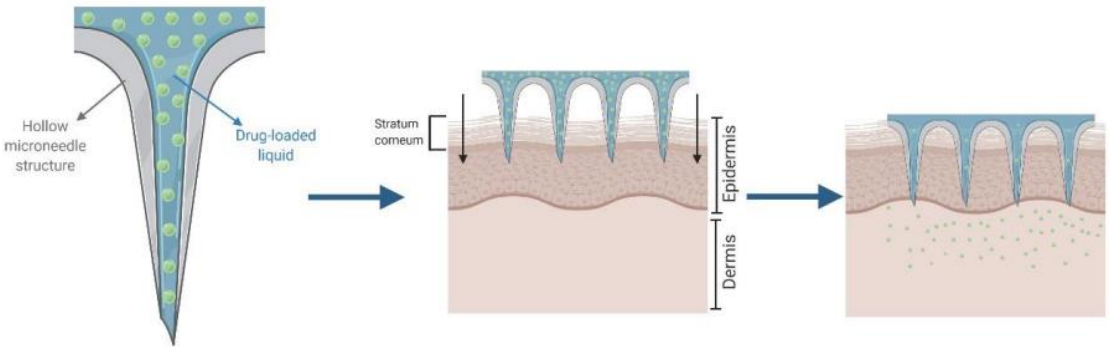


Figure 13

HYDROGEL FORMING MICRONEEDLES

These sort of microneedle is a very new invention. Microneedles are made from super-swelling polymers. Hydrogel-forming MNs or swellable MNs have been developed as an alternative to Poking and Packing techniques. The main goal of these devices is absorption of the fluid of skin which can produce microchannel which is at regular period. These channels are unblockable between dermal capillaries after insertion. This process is for the very less potent drugs. This type of needles has hydrophilic structure which later allows them to absorb a very good amount of water into their networked structure. They are good in terms of their size and structure. They could be easily sterilized and removal is very rare. Many scientists have researched for needles which can deliver metformin drug through topic route which can reduce the problems which occurs with oral administration. The use of specially developed microneedles increased the drug's penetration and bioavailability.

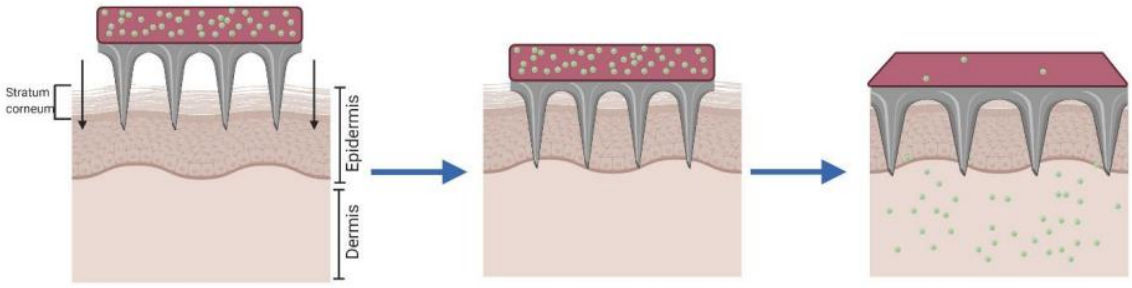


Figure 14

FABRICATION OF MICRONEEDLES

When constructing a microneedle, the microneedle's goal is taken into account initially. The drug kind and dose, as well as the desired pharmacodynamic and pharmacokinetic and goals, are all taken into account. After that, the best microneedle design and materials are chosen. Microneedles are produced in various techniques, depending on the design or content. MEMS technique is the most effective for fabricating the ideal structure of MNs for a specific usage, as it enables for exact duplication of MNs to make incredibly small devices. Microfabrication enabled the manufacture of these extremely small structures, thanks to the microelectronics sector. Microfabrication techniques were used to develop the first MNs. Since then, many different products have been used, including polydimethysiloxane, ceramic, glass, titanium, dextrin, polymers, stainless steel. There are three essential procedures in this technology that is deposition of film material on any surface, etching is to be done, and photolithographic imaging.

LASER CUTTING

Metallic microneedles are produced from stainless steel using this process. Metallic sheets are cut to micron-sized needles shape using laser, and the structure and alignment of the arrays are sketched using software. Using this laser, the desired shape of microneedle can be generated from sheet. Electropolishing can be used to clean needle tips or rough surfaces.

LASER ABLATION

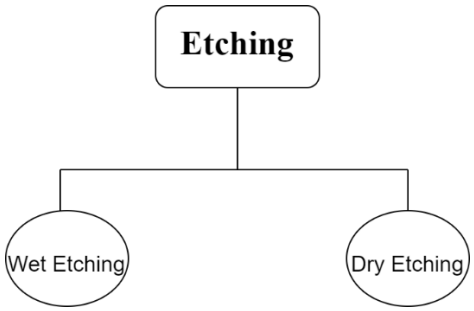
It is used in producing solid metallic arrays. Metals like titanium, in addition to stainless steel, are fabricated. Protuberance forms in the center of the surface being handled after deposition of light. Overlapping light pulses can be used to give the center protuberance a suitable shape. The protuberance transforms into a needle with a height of roughly 10 micrometers after three pulses. Laser cutting creates a 2D shape out of a metal or polymer plate, whereas laser ablation creates a 3D shape out of the plate.

PHOTOLITHOGRAPHY

In order to produce solid or hollow microneedles, photolithography is used which is a popular method nowadays. Silicon or dissolving/hydrogel microneedles are produced using inverse mould method in which a photosensitive polymer is allowed to cover silicon substate. So , when the photoresist comes in contact with ultraviolet rays it manipulates the polymer's "cross-link" bonds and so the solubility of the polymer section exposed to UV varies and after which photoresist is removed.

ETCHING

Etching is a key procedure for establishing the tapered shape of a microneedle tip when it is manufactured using conventional photolithography. Before etching procedure to be conducted various dimensions of microneedles are determined well in advance. Following that, the etching procedure is used to determine the length and shape of the microneedles.



DRY ETCHING – There are various physical (beam milling) and chemical methods (ion etching) used for preparation of microneedles. Silicon needles produced by dry etching may be solid or hollow. In this method inert gas is passed which ionizes by electrodes in dry etching. In Anisotropic etching the ions impacts the substrate. Chemical approaches include high-pressure plasma etching, which involves generating a chemically reactive plasma gas. Isotropic etching can be achieved when volatile material produced from the reaction of plasma and substrate.

WET ETCHING – Microneedles are produced and sharpened using this procedure. Metallic and silicon arrays are both made with it. The surplus material is removed from

the substrate. Dynamic etching and Static etch are the stages of Wet etching, In first phase etching occurs of isotropic substrate, as well as strong etchant replenishment while in second phase, tops of the Microneedles are produced. The etching is more intense at the top of the columns than it is at the bottom. Wet etching is faster etching rate than dry etching as it is a chemical reaction.

E) FABRICATION TECHNIQUES AND MICRONEEDLES PRODUCTION TYPES

	TECHNIQUES	**MICRONEEDLES PRODUCTION TYPES**
a)	Laser Ablation	Solid Metallic
b)	Laser Cutting	Solid Metallic
c)	Photolithography	Dissolving , hydrogel forming, Solid ceramic
d)	Dipping	Coated Type
e)	Spraying	Coated Type
f)	Pulling Pipettes	Hollow Glass
g)	Vapor Deposition	Solid Silicon
h)	Metal Electropolating	Solid Metallic
i)	Drawing Lithography	Hollow Type, Dissolving
j)	Microstereolithography	Solid Metallic, Solid Silicon
k)	X-Ray Lithography	Dissolving , Hollow type
l)	Dry Etching	Solid Silicon

m)	Micromolding and melt casting	Dissolving , Solid Ceramic
n)	Wet Etching	Solid Metallic
o)	Droplet Born Air Blowing	Dissolving
p)	Photon Polymerization	Dissolving , Solid Ceramic

Table 2

F) 3D PRINTING TECHNOLOGY

3D printing is a low-cost, elevated additive processing tool for rapidly prototyping a design. The manufacturing of microstructures such as microneedles has recently been added to the 3D printing technique. Due to recent advances in the field on science, using 3D printing sophisticated microneedle preparation can be possible. There are various modelling methods used for the formation of microneedle preparation. The 3D printing materials are specific. 3D printing has the potential to have a qualitative as well as a quantitative impact on the microneedle business, by supporting the concept of personalized medicines, as production shifts from mass to individual. Such technologies make it possible to build a product that is cost-effective and quick dependent on the application. Individual patient demands can be considered, and multifunctional therapies can be coupled in bespoke systems without requiring large changes to production lines. Overall, 3D printing is a better option over conventional into which through skin only drug could easily administered and reach to target, Also it provides personalization and a better substitute of traditional manufacturing techniques.

G) APPLICATIONS

OLIGONUCLEOTIDE DELIVERY

Short DNA or RNA molecules are referred as oligonucleotides. It's tough to get oligonucleotides to their intracellular sites of action. The microneedle method was used to deliver a 20-mer phosphorothioated oligodeoxynucleotide. The poke with patch method was used to deliver oligonucleotides using microneedles. In comparison with intact skin, more medication was observed to penetrate. When iontophoresis was combined with a microneedle technique, the results were better than when iontophoresis was used alone**.**

VACCINE THERAPY

A biological preparation is referred to as a vaccination. It delivers disease-specific active acquired immunity. Vaccine therapy activates the body's immune system and provides protection from future microbe encounters. In vaccine therapy, the microneedle technique was found to be effective. A microneedle was used to administer the DNA vaccination. Immune responses were far superior to those found with standard doses. Scientist have tried to make hollow microneedle for the delivery of influenza vaccine in order to overcome the cost as the amount of drug required for intramuscular injection was too high as compared to microneedle. Thus, microneedle is more effective for vaccine delivery. The use of hollow microneedles to administer anthrax and rabies vaccines was also investigated. The drug's precise administration in the upper dermis boosts immunity. Intradermal vaccination using dissolving microneedles was also studied.

PEPTIDE DELIVERY

When peptides are ingested orally, they are enzymatically destroyed. Peptide administration by microneedles can aid in peptide penetration into the skin. Desmopressin is a strong peptide hormone that is synthesized from vasopressin. Diabetes insipidus is treated with this medicine. The use of microneedles to deliver desmopressin was investigated to be found effective and risk-free. A antibiotic which treats various skin

conditions (Cyclosporin A) was delivered using microneedles into the pig skin for a hour, resulting in the dissolution of approximately 65 percent of the microneedle and the delivery of 34 6.5 g of medication. Liu et colleagues produced GAP- 26 gap junction blocker infused polyethylene glycol diacrylate derived microneedles for delivering peptides via the swelling effect in one investigation. The penetration of loaded peptide by the proposed microneedles was improved, which was proven by the reduction of keloid fibroblast proliferation and collagen I expression.

HORMONE DELIVERY

Insulin is a hormone consists of peptides. Microneedle insulin delivery was found to be more effective at lowering blood glucose levels . Li et al created solid microneedles and investigated how they affected blood glucose levels and insulin delivery in diabetic mice and it showed that there was one third reduction into level of glucose in mice. Which clearly demonstrate that microneedle have improved insulin permeability through skin. Microneedles coupled with pancreatic-cell capsules that sense sugar levels and produce insulin were studied by Ye and colleagues. However, the patch was determined to be ineffective in comparison to conventional injection for parathormone.

COSMETICS

The use of microneedles in cosmetics is getting more popular, particularly for improving skin texture and treating blemishes and scars. The microneedle method was used to administer various cosmetic active substances such as *vitamin* C, 2-difluoromethylornithine hydrochloride alpha-difluoromethylornithine hydrochloride and *vitamin A.* Melanin along with phosphatidylcholine liposomes (nanoliposomes), resulting in improved lipid solubility. When using an e-roller, the pigment moved deep inside the hair structures.

LIDOCAINE DELIVERY

Lidocaine is a local anaesthetic agent. When compared to a hypodermic injection, microneedling lidocaine generates less pain and hence improves patient compliance. Lidocaine was applied to the microneedle tips by Baek et al. These microneedles showed constant skin penetration in vitro and improved drug delivery in 2 minutes. As a result, microneedles can be employed to provide painless and quick local anaesthetic. Microneedles covered with PEG-lidocaine dispersions delivered more medication in 3 minutes than topical formulations in one trial.

PAIN THERAPY

Meloxicam polymeric microneedles are made of Polydimethylsiloxane moulds. While conducting experiments tells that in order to release full drug it takes 1 hour time. But its penetration increases to 2.58 times when it is free drug solution . Neuropathic pain can be difficult to manage. The use of dissolved microneedles to alleviate neuropathic pain was investigated. These supplied a specific calcitonin gene-related peptide (CGRP) antagonist peptide with good receptor selectivity. There is no adverse effect of this. A drug administration through microneedle has created enormous prospects for the pain treatment industry.

OCULAR DELIVERY

Drug delivery targeting can be used to treat a variety of posterior segment conditions. Nanoparticles were delivered through the suprachoroidal space using iontophoresis. More than quarter percentage nanoparticles were transported to eye when they are coupled with microneedles.

CANCER THERAPY

Every year, cancer strikes a large number of people around the world, and cancer treatment is fraught with difficulties. Microneedles have been studied for the delivery of anticancer medicines. A transmembrane protein in the Ig superfamily expresses T cells was delivered using biodegradable microneedles. That microneedle is pH-sensitive and made of dextran. When the cream was administered to skin that had been treated with

solid microneedles, the permeation of 5-fluorouracil was increased by up to 4.5 times. Microneedle effectiveness was further demonstrated by significant reduction of tumour development. The negative effects of these medications could be reduced if they were delivered locally. Skin cancer and localised administration of anticancer medications were also explored using polymeric microneedles.

H) MICRONEEDLE MARKET PRODUCTS

NAME OF PRODUCT	MANUFACTURER	DESCRIPTION	USE
Dermaroller	White Lotus, Germany	Metallic Microneedle	Improves Skin texture and pigmentation
LiteClear	Nanomed Skincare, United states of America	Solid Silicon Microneedle	For Acne and skin problems
C-8 (Cosmetic type)	The Dernaroller Series	0.13mm Needle	Increase topical Agents penetration
MicroHyala	CosMED , Japan	Dissolving Microneedle	Contains Hyaluronic acid to treat wrinkle
Micron-jet	Nanopass technologies ltd , Ness Ziona, United states of America	intradermic Injection	For painless drug delivery
MicroTrans	Valeritas Inc , NJ , United states of America	Patch of micronnedle	Transdermal *Drug Delivery*

MS-4	The Dermaroller Series	0.13mm Needle	For Scars (Facial Acne)
Soluvia	*Becton, Dickinson* and Company, NJ, United states of America	Hollow Microneedle	Accurated intradermal delivery of drug
Macro-flux	Zosano Pharmaceuticals, CA, United states of America	Microneedle (Metal)	Peptides and vaccines delivery
VaxMat	TheraJect, United states of America	Dissolving Microneedle	To Deliver Macromolecules
Nanoject	Deviotech, Switzerland	Microneedle Based Device	Dermal Drug Delivery

Table 3

SkinPen

The first only FDA-approved device is the SkinPen . The SkinPen is a microneedling device with many tiny needles that can be used on the skin. The one only device that has been validated to use sterile, straight needles with accurate depth control is the SkinPen. Heat and chemicals are not used to target the skin's natural collagen. Reduce the occurrence of ageing for skin that appears more young. To achieve overall skin renewal, reduce the appearance of face acne scars. At a rate of 1600 per second, SkinPen generates micro-channels (microscopic holes). These wounds stimulate your skin, speeding up the healing process. The outcomes are perfectly safe for all types of skin and kinds because SkinPen does not use heat or chemicals. The SkinPen therapy is meant to activate the skin's natural healing mechanism in three simple steps : Inflamation - The microneedles in the SkinPen penetrate the skin's surface, initiating a natural immunological response that disinfects, removes debris, increases blood flow, and stimulates the formation of new tissue. Proliferation - SkinPen creates micro-channels or microscopic holes that are repaired with new granulation cells

that contain collagen proteins. In addition, a new blood vessel network emerges. Remodelling - Collagen and elastin proteins are abundant in new skin tissues and blood vessels. These proteins improve skin quality by minimising facial acne scars and neck wrinkles, making skin look smoother, more vibrant, and younger.

I) ADVANCES IN DRUG DELIVERY BY MICRONEEDLES

Physical approaches which are used to enhance drug distribution and drug penetration using microneedles are as follows:

1. Iontophoresis
2. Sonophoresis
3. Electroporation

J) COMBINATION OF IONTOPHORESIS AND MICRONEEDLES

In this method using electrical current drugs are transported via skin. The preliminary benefit of employing iontophoresis with microneedles is that the current may be controlled to manage drug distribution. It was investigated that this method can be used to deliver insulin unilamellar nanovesicles. With the use of iontophoresis and microneedles, the nanovesicles' positive zeta-potential and low diameter increased insulin penetration.

K) COMBINATION OF SONOPHORESIS AND MICRONEEDLES

Ultrasound is used in sonophoresis which improves the efficiency of drug delivery by creating cavitation and by altering internal structure of skin. The frequency is adjusted to manage the degree of drug penetration for various drugs. Chen et al. discovered that utilizing a combination of sonophoresis and microneedles, they were able to improve the efficiency and delivery range of calcein and bovine serum albumin.

L) COMBINATION OF ELECTROPORATION AND MICRONEEDLES

Using high voltage current for short duration upon skin to generate aqueous routes by causing localized disturbance. This method was also utilized to improve the penetration of bigger molecules. In order to eliminate the use of electrode , each microneedle roles as electrode. Wilke and colleagues developed silicon microneedle which targets the tumor cell for drug to acts upon it using temperature and fluidic system.

M) COMBINATION OF MICROPUMPS AND MICRONEEDLES

When combined with microneedles, micropumps allow precise drug delivery. In order to regulate the drug to specific target with specified timing , pumps plays a vital role in maintaining rate of flow as well as pressure. Zahn et al. developed an system that could control fluid extraction for medical analysis while also administering drugs in response to metabolite levels.

N) CHALLENGES AND FUTURE PROSPECTS

While discussing challenges of microneedles, its major concern is with its safety and efficacy. Some results into skin irritation, allergies, skin rashes, while other produces hazardous waste after application can be seen on implication of this technology. As it with holds a minute quantity of hydrophilic drug, it is difficult to make it reach to the target of action. Thus, a sustainable needle with sufficient amount of sustaining strength and one which upholds force must be used so that drug could penetrate the skin. As, it must first puncture the skin and then stick to surface of skin, if its not adhering then it might create the risk of infection. It really needs a furthermore improvements so that a patient must be compliances with the new technology and trust it to reuse. There is lots of research going on microneedle to improve the technology in order to commercialize it well in market with limited cost and fulfilling all regulatory obligations. Furthermore, research will surly lead the microneedle as a promising technology in drug delivery in near future.

6. IONTOPHORESIS

A) INTRODUCTION

Iontophoresis is a technique that uses an externally generated capacity difference to promote ion transport across a membrane. The procedure is known as transdermal ionto-phoresis when the membrane in question is skin. The SC, the topmost sheet of the epidermis with a diameter of about 11-110 m, is the primary barrier to molecule movement into and across the skin. The SC is made up of numerous sheets of corneocytes keratin-filled cells with a nucleus cut in a lipid matrix, which acts as a continuous medium through the S C and is organised mostly in bilayers2,3. Ceramides, cholesterols, and free fatty acids make up roughly equal amounts of intercellular lipids.

The internal (transcellular) pathway through the cells, the paracellular transit into the conneocytes along the lamellar lipids, or the shunt pathway via hairfollicles, sweatducts, and secretaryglands can all happen at the same time.

Ions seek paths with the least amount of electrical-resistance, which in the SC is thought to be through the holes. Some studies suggest that these holes are sweatglands, while others claim that transport happens via the two hair follicles and sweat glands.

The contribution of the follicular and non-follicular modes of penetration is influenced by the physicochemical qualities of the molecules. Lipophlicmolecule are predominantly found in the lipid inter-cellular areas of the SC and the lipidmembranes of epidermal keratino-cytes, whereas hydrophilic molecules are mostly found in hair follicles. Chemical & physical enhancement strategies have developed to improve passive-transdermal penetration of the majority of medicines in order to obtain clinically relevant plasma-concentrations. One physical ways is ionto-phoresis.

Cationic or neutral therapeutic agents are under the negative terminal, whereas negative-therapeutic agents are placed under a positive terminal, in ionto-phoresis. Ions are replaced into through the skin when a low voltage and low current density is applied,

according to simple electrorepulsion. The anode (active electrode) drives cationic medicines into and through the skin while also extracting anion from the tissue beneath the skin. Negative buffer ions are pushed in the skin at the negative terminal (return electrode), and positive ions from the tissues are extracted into the negative terminal. (fig. 1) Depending on which drugs or molecules are utilised, it is also conceivable to put an additional charged drug in the return electrode to be supplied simultaneously, or to use a mixture of pharmaceuticals in the active electrode to enhanced the intended effect or boost skin permeability.

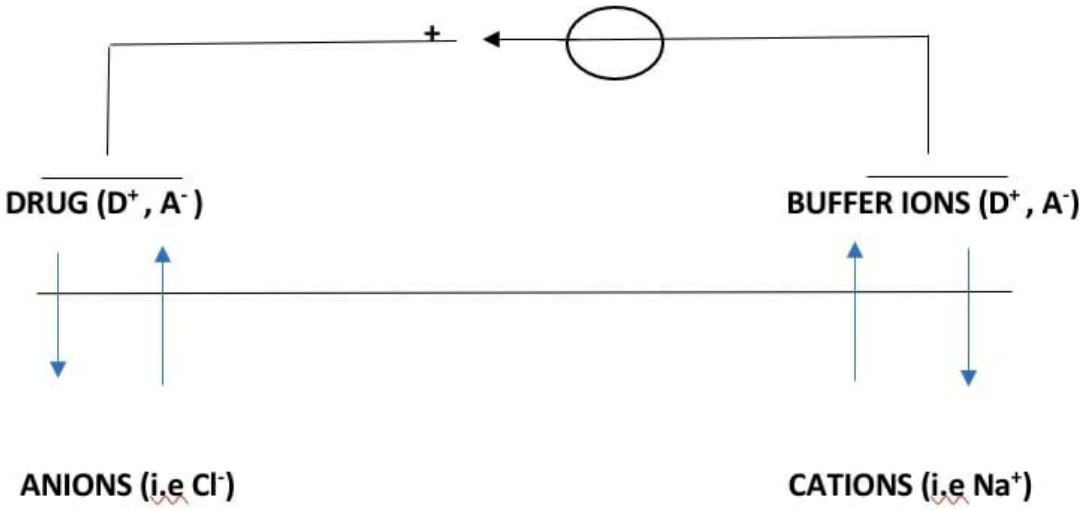


Figure 1 Transdermal iontophoretic system.

Figure 15

Electrically assisted transdermal delivery is a more formal term for transdermal ionto-phoresis. Iontophoresis also known as electron repulsion, electromigration, or the NernstPlanck effect is one of three key boosting techniques for drug flow via the skin. The electoro osmotic flow and current-induced increase in skin permeability, commonly

known as the damage effect, are the other mechanisms. Electro-osmotic flow is flux or more fluid that is inspired by a voltage differential threw a charged membrane, and it always flows in the same direction as counter ions. The counter ions are cations because, human skin is negatively charged under physiological conditions, and the electroosmotic flow is therefore from a positive terminal to a negative terminal. As a result, anions cathodic delivery is hampered, whereas cation anodic delivery is aided by electrosmosis.

Electroosmosis is responsible for the enhanced mobility of neutral molecules during ionto-phoresis. All of the foregoing mechanisms influence ions, hence electroosmosis contributes positively to the transport of positive ions and negatively to the transport of negative ions under normal physiological conditions. The effect of electroosmosis on ion transfer grows in proportion to the ion's size.

The electrorepulsion effect increases the flux of tiny lipophilic cations the most. When the ionic drug concentration is more enough that the drug take the majority of the current, electro-osmotic flow have a negligible effect on drug flux.

Both local and systemic medication administration have been achieved using transdermal ionto-phoresis. Antiinflammatory medications, such as ketoprofen31, can also be administered by transdermal ionto-phoresis in subcutaneous layer, subcutaneous tissues, and joints. some systemic medications are still being studied using iontophoretic administration. Fentanyl, an analgesic, tacrine III, a regenarated cholinesterase inhibitor, and many insulin formulations are among them. Iontophoresis has been used to extract information without the requirement for the blood sample due to its symmetrical nature, in which ions are pushed both into and out of the body.

B) HISTORY

Iontophoresis, derived from the Greek "ionto" meaning "ion" and "phoresis" meaning "to bear," is a method that uses a low electric current to improve the penetration of an ionised molecule across or into tissue. Clinical application of current can be traced back to the ancient Greek civilization's golden age, and was most likely invented by Varatti in 1747.

C) ADVANTAGES AND LIMITATIONS OF IONTOPHORESIS

For its enhancing effects on skin permeability, ionto-phoresis provides a non-invasive approach for the delivery of a wide variety of drugs at therapeutically meaningful levels. It shares the maritss of trans-dermal drug delivery, namely the avoidance of hepatic first-pass effects and the harsh environment seen in the gastro-intestinal tract when utilized transdermally. These maritss are especially important for the administration of proteins and peptides that are not able to acquire therapeutically relevant quantities by oral drug delivery. Because it reduces the period between administration and transport to the target tissues, ionto-phoresis enables for good delivery of medicines having short biological halflives. Due to the general infrequent dosing, patient compliance is considerably enhanced, and the treatment can be stopped at any time. This method also allows for a high level of programm-ability, as treatment may be monitored and altered at pre-programmed rates that can be tuned to the patient's needs. This programm-ability, along with the fact that drug distribution is directly dependent on the ,in a large reduction in drug level fluctuation.

The benefits of ionto-phoresis are counterbalanced by its drawbacks, the most prominent of which is the risk of irritation and pain when the electric current is applied. Although the procedure is thought to be safe, increasing the applied current's intensity might cause

is not the same in the deeper layers as it is at the surface for ionic chemicals, and fluctuations (from 4 - 7.3) occur during transdermal transport. Because of the effect of pH on ionization, this could result in ineffective ionto-phoresis for specific compounds. This phenomenon may be specially critical for peptides and proteins, which rely heavily on charge for distribution and stability. Due to the existence of other charged moieties, good iontophoretic delivery of charged species may be hampered by an ion compatative factor. Furthermore, drug breakdown or adsorption under the electrode has been a key worry. Finally, developing a device that is low-cost, safe, and convenient while ensuring therapeutically relevant doses may be difficult.

D) IONTOPHORETIC MECHANISM

It's principal is like "opposite charges attract"and "like charges repel". A set of electic terminal is utilised to generate these repulsive forces and attractive forces, which supply the outer energy needed to move ions via the skin and improve medication permeability. These concepts have main to the development of 2 principal systems: negative electrode and positive electrod ionto-phoresis, both of which consist of a basic iontophoretic setup with an anode and negative terminal electrode pair, Positively charged ions can be given by placing them under the anode due to repulsion, while the negative electrode is on the distal spot on the skin to create an attractive force. -VE charged ions from the body (mainly Cl) flow to the direction of the anode at the same time. Anodal ionto-phoresis is the name for this technique, and Figure 4.1 shows a typical configuration. The electrodes are reversed for cathodal ionto-phoresis, which delivers a negatively charged medication through the skin. Figure 2 shows an iontophoretic system with silver–silver chloride (Ag/AgCl) electrodes. To manage electroneutrality, either a positive ion from this compartment travels into the skin, or an anion from the skin moves into this chamber.

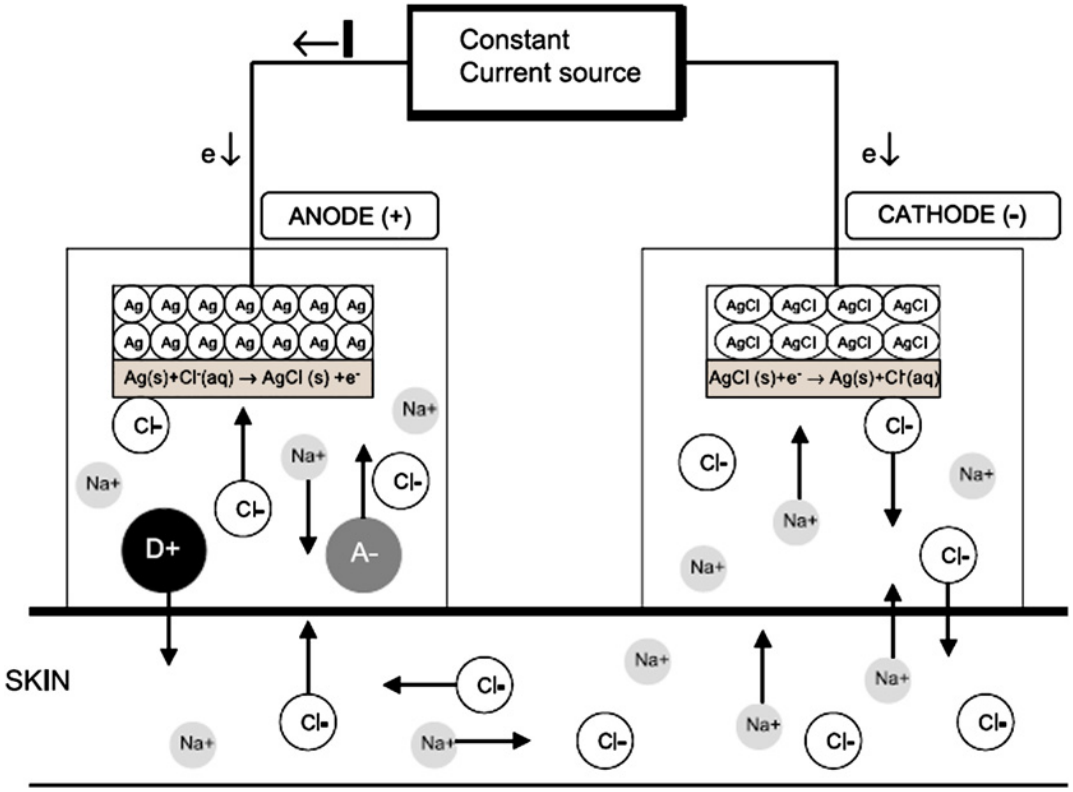


Figure 16

The silver and silver cloride system is the widly used electrode system for a variety of reasons. For starters, this pair of electrodes is resistant to pH variations, which is one of the most important prerequisites for effective ionto-phoresis. Because the silver and silver chloride combination are reversible electrodes, the electrical and clemically mix processes that take place happen at lower voltages than those necessary for water electrolysis, eliminating pH fluctuations and boosting drug delivery efficiency.

Higo et al. (2001) developed a again usable ionto-phoresis electric terminal device to prevent metal from the electrode from entering the body. It further states that throughout operation, there is no change in pH or voltage current no fluctuation. Depolarizers (potassium iodide, ascorbic acid, thioglycolic acid and others), pH regulators

(calcium oxide, hydroxyapatite, zeolite, and others), & OH can all be found in this electrode component as an electrolyte.

E) PATHWAYS AND FACTORS AFFECTING IONTOPHORETIC TRANSPORT

Transcellular, paracellular, and trans-appendageal are the three basic pathways of passive skin permeation (Figure 3). The transappe-andageal and jounction routes are thought to be the primary routes for iontophoretic transport, with such as hair follicles and sweat glands being the primary transport way. Several techniques, including vibrating probe electrodes and visualization techniques such as transmission electron microscopy with mercuric chloride and laser con-focal microscopy, have been used to determine the dominance of this trans-appendageal ionto-phoretic transports. Iontophoresis can further improve skin delivery by causing capacity-dependent holes creation in the stratum cornium, which is linked to a "flip flop" gating mechanism caused by the remodelling of polypeptide helices when an electric current is applied.

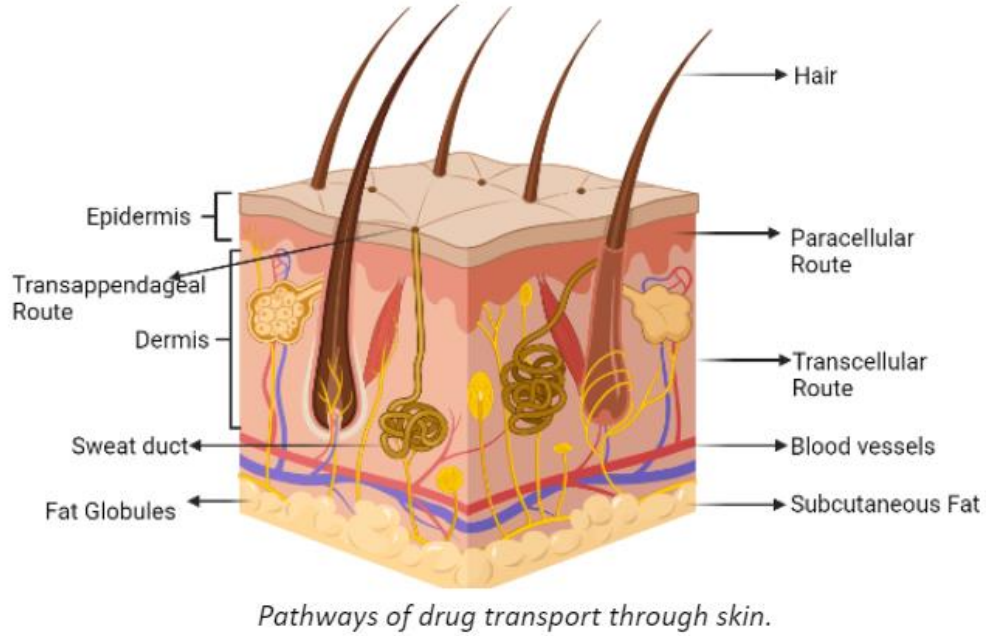


Figure 17

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Prem Patel

Figure 3

Despite the fact that iontophoretic transport can provide a 100-fold improvement over passivediffusion (for plus ions with the relative molecular size of unity), the efficiency of iontophoretic transport is repeatedly not more than 100 % due to a number of factors that influence the transport efficiency, most notably the propertie of the proper, the vehicle and other formulation factors, the membrane, and other system components.

F) PROPERTIES:

competing ions, Concentration, & molecule size

Several investigations have demonstrated that as the drug concentration rises, the iontophoretic flux rises as well. The concentration–flux profile, on the other hand, frequently displayed a curved pattern that no change after a period of activity as the concentration was increase. During the iontophoretic deliverys of apomorphine between the human SC, VanderGeest observed a plateau in flow profiles. This was attributed to the donor reaching the maximal solubility concentration of apomorphine and skin resistance generated by increasing apomorphine concentrations. The presence of participated ions, such as same charge or counter-ions from the formulation, the presence of a buffer used to maintain pH or autogenous ions, can also reduce the drug concentration effect of on flow. The major drug ion's transport number is reduced as a result of competition from other ions, specially if the compet ions are more variable, such as those found in buffers. The permeant's molecular size is also a significant contributor to the iontophoretic flux. Regardless of whether the solutes are positively charged, negatively charged, or uncharged. With increasing molecule size, the contribution of electroosmosis to the iontophoretic flux complicates the situation even further.

PH, CURRENT

In ionto-phoresis, pH is crucial because it keeps a major amount of the medication in its ionised form. Several studies have proven the role of pH in the efficacy ionto-phoretic transport. When lignocaine was un-ionized, found that the indirect diffusion flux is high and the iontophoretic flux was low. The flux rose by 4 and 8.5 times pH values of 5.2&3.4, respectively, where medications are becoming more and more ionised. In the ionic medication distribution of proteins and peptides, pH is particularly crucial since it can influence the net charge on these molecule base on their iso-electric points. Furthermore, flow is regulated by the pH of the membrane (skin), which find out from the electro-migration and electroosmotic contribut to the flux.

Larger current densities, on the other hand, are limited by saturate occurrence that occurs with more currents, as well as the risk of producing skin pain and irritation.

For threw the skin distribution of cytochrome C covering pig skin, CazaresDelgadillo used continous-current ionto-phoresis. They discovered that whereas the flux rose linear with the provided current at lower current densityes, the flux values of cytochrome C at 0.3&0.5 miliAmper/ cm2 were not analytically different, owing to a fullness phenomenon occurs next, not more then transport number is reached.

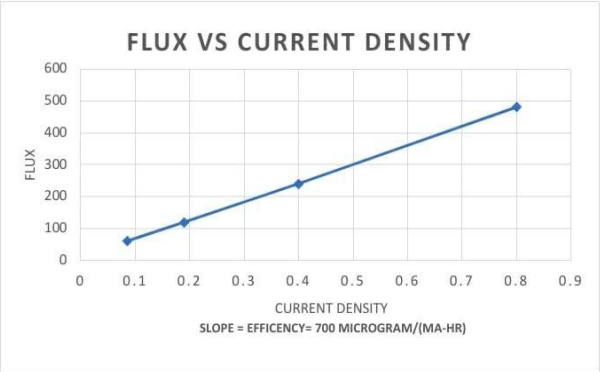

Figure 4 At a methylphenidate concentration of 0.5 M (pH 14 3.5, n 14 4) there is a relationship between applied current density and methylphenidate iontophoretic flux.

Figure 18

Iontophoretic device use either continue-current or stoped-current systems, and both have been successfully use in, in vitro and in vivo experiments . Despite comper, the merits of one sort of live profile over the other has yet to be proven. When defferencited to steady DC current or AC current, a beats DC profile was found to be more effective in delivering Lutenizing hormone-releasing hormone and nafarelin across the person epidermis (Raiman et al., 2004). For the across the skin penetration of Ketorolac tromethamine through rat skin, Tiwari & Udupa discovered that steady DC was more potent than pulsed current.

Models for iontophoretic delivery have attempted to numerous factors that influence delivery in order to account for the various factors that influence iontophoretic transport. Some models, such as the StokesEinstein and without volume models , have characterised finite variables, such as the link between diluent size&structure and ionto-phoretic transport, but others, such as the ionic mobilityhole model, are more comprehensive. The size, mobility, and concentration of the solute, the applied current, interaction of solute molecules with pore walls and subsequence restrictions of the pore that all are include in this model.

G) REVERSED IONTOPHORESIS

Reverse ionto-phoresis is a method that involves applying a tiny electrical current to the skin, typically less than 0.5 mA/cm2, to remove analytes (charged and uncharged). Electro-migration of charged molecules to the electric terminals of different polarities, electroosmosis of neutral molecules to the negative terminal, or a mixture of the two for cations, are the mechanisms of extraction. Because the procedure is really non-invasive, it should be considered as a viable substitude to blood sample for drug observation. It was developed using reverse ionto-phoresis. that

Other uses has been proposed for drug observation and to chacking purposes as well as substantial efforts to increase extraction efficiency . The capacity of these noninvasive biological sampling approaches to quantify low amounts of analytes reliably and precisely would be one of its limitations. Only one gadget of this type has been commercialised to date (GlucoWatch Biographer).

Sekkat investigated the suitability of utilising back ionto-phoresis to observ two models medicines commonly given to premature neonates: caffeine and theophylline. The back iontophoretic removal of the two medicines over the skin to both the negative terminal and positive terminal rose linearly with time, according to their findings. Both medications, extraction to the negative terminal was substantially higher (t-test, P 0.05) than extraction to the negative terminal. The higher to lower diffusion of the two medicines across unbroken skin was so tiny that it was impossible to detect. Electro-osmosis, or a convective dissolve in another substance flow in the direction of counterion action from the positive terminal to the negative terminal, was found to be the primary mode of electrotransport.

Wascotte investigated the technique's capatiti for non-invasively measuring urea and potassium levels, as well as tracking their concentrations during hemodialysis. These in vitro investigations showed that reverse ionto-phoresis can extract urea and potassium quantitatively and proportionally, even when the analytes' subdermal concentrations changed over time. These findings suggested that non-invasive potassium&urea monitoring to diagnosis kidney failure during hemodialysis is possible, but that in vivo measurements are required. In reverse ionto-phoresis applications, Wascotte studied the use of a thermally reversible gel as a gatherer vehicle. The findings demonstrated that thermally reversible polymer solutions can be employed as a gatherer vehicle in reverse ionto-phoresis applications to provide a straightforward and convenient manner of handling samples.

H) INTOPHORESIS APPLICATION

Transdermal ionto-phoretic devices offer the capacity to improve medication delivery to therapeutically meaningful levels. They also allow for the programming and control of drug kinetics via the device, which improves patient compliance. These characteristics allow the system to deliver a broad spectrum of the compounds, including those macromolecules with low passive permeability. Iontophoresis has been shown to improve transdermal penetration of various small compounds, rotigotine, buspirone hydrochloride, sodium salicylate, hydrocortisone, lidocaine, and buprenorphine, when combined with other approaches.

Ionto-phoretic drug delivery methods has also piqued interest as a means of improving macromolecule distribution, like insulin parathyroid hormaone and peptide delivery. This molecule is frequently polar, has a charge, and is incapable of being delivered orally due to less absorption and stability. Insulin has long been a popular iontophoretic delivery candidate, and it has been extensively studied, mostly in conjunction with chemical enhancers before treatment or other enhancing approaches. The majority of these investigations resulted in a significant increase in insulin flow and, in many cases, therapeutic dosage delivery. Similar findings were recently published by Akimoto et al. (2006), who discovered that the ionto-phoretically accelerated skin penetration of insulin increases linear with the density of provided pulsed DC current. Iontophoretic transport has also been explored in other macromolecules including LHRH and nafarelin. The charge, molecular weight, whiteout water, and, most importantly, the physical and chemical stable the product of the peptides in the delivery system, as well as the skin's proteolytic movement, all have a significant impact on the efficiency of transdermal ionto-phoresis of peptides. Eljarrat- Binstock et al. (2005) found that ionto-phoresis could be useful in drug distribution via additional channels such as transcorneal and trans-scleral. The results of dexamethasone tran-scorneal ionto-phoresis in the rabbit showed that a 30fold greater concentration was written down in the cornea after a

short iontophoretic treatment of one milliampere for only one minute after that the conventional treatment of numerous drop instillation (every 5 min for 60 min).

In vitro studies of tran-sungual ionto-phoretic transport of the neutral permeants MA and UR, as well as the positively charged fixed TEA, across fully hydrated human nail plates, have recently been published (Hao et al., 2008). A greater current of 0.3 mA resulted in improved transport of neutral charged permeants over the fully hydrated person's nail plates, while a lower current of 0.1 milliamperes resulted in significantly improved transport of positively charged TEA. These findings suggest that utilising an iontophoretic drug delivery system, it is acceptable to boost the flux of a therapeutic molecule over the nail plate to treating nail infections.

I) CURRENT AND FUTURE DEVELOPMENT

Several variables are driving drug delivery innovation, adding an older patient, bio-logical pharmacological therapy for the chronic disease , and a focus on patient selfmonitoring and selfcare. In the coming decades, there is no question that the skin will again become one of the primary path of medication delivery. Iontophoretic systems that use an electrically driven penetration augmentation method has been found to be a promising technology for adminstrating diverse compounds, including macro-molecules, despite the SC's formidable barrier. Iontophoretic drug delivery systems account for the bulk of the some physically improved transdermal delivery methods that have been developed and marketed to date. The device's net efficiency, mobility, and ease of administration are the most important elements in commercialization.
IOMED's new Hybresis Iontophoresis Drug Delivery System are some of the most well-known devices (see Table 4.1). Vyteris Inc. have acquired FDA approval for LidoSite, a firstofitskind technology which has lidocaine hydrochloride and epinephrine bitartrate. This thing includes a LidoSite Patch, a LidoSite Controller, and a battery-powered, micro-processor-controlled DC source for local analgesia during superficial dermato

logical operations. The FDA-approved ETRANS fentanyl hydrochloride system from Alza Corp is a patient-controlled, FDA-approved option for acute pain management in a medically supervised setting. The ability to design it to provide predetermined doses and an "ondemand" button, which allows the patient to take the drug as needed, are two of the device's maritss. The IOMED Hybresis System is a minicontroller and patch system with no lead wires that can provide inclinic therapy in 3 minutes. The 3-minute Skin Conductivity Enhancement function reduces the skin's resistance quickly and normalises or making patch-only wear duration is short and more predictable.

Company	Device	Molecule	Application
Alza Corp.	E-TRANS^{R}	Fentanyl Hydrochloride	Pain management
Vyteris Inc.	LidoSite^{R}	Lidocaine Hydrochloride	Pain management
Ortho-McNeil Inc.	IONSYS^{TM}	Fentanyl	Pain management
Animas Corp.	Gluco Watch^{R} G2 Biographer	Glucose	Monitoring glucose

Table 4

Combining passive transdermal delivery with different physical enhancement methods like electroporation, chemical-enhancers, micro-needles, ultrasound, ionexchange , lasers, materials, blades or high temprature has resulted in slightly higher flux levels than passive transdermal delivery or any of the techniques alone. with tailored drug input rates and the ability to stop drug transport as necessary. The skin irritation caused by combination techniques, on the other hand, could be a matter for concern. Most clinical trials have thus far focused on smaller molecules like metoclopramide plus hydrocortisone, cortisone, and fentanyl. and attention of deficit hyperactivity disorder and pain treatments.

7. Needle Free approach

A) Introduction

Injections are a common way to deliver medications to prevent and treat a variety of disorders. However, because it induces tissue damage, it is an invasive technique of drug administration. Injections, especially when needles are re-used and administered inappropriately, can be a cause of disease transmission.

Needle free injection technologies (NFIT) have grown in favour in recent years as a way to avoid the drawbacks of needle-based injections. They have a number of advantages. These technologieas are designed for injecting solid formulations as well as solid particle dosage forms of medications and vaccinations.

NFIS are an innovative approach to provide medications to patients without penetrating their skin with a needle. Marshall Lockhart initially described needle-free methods in his patent jet injection in 1936. scientists created high-pressure "guns" in the early 1942s, which used a fine jet of solid to puncture the skin and deposit the medicine in the underlying tissue.

B) Principle

NFIT uses energy that is strong enough to drive a premeasured amount of a certain medicine formulation, which is placed into specific "cassettes" that may be. These forces can be generated in a variety of ways, including high-pressure fluids, gases.

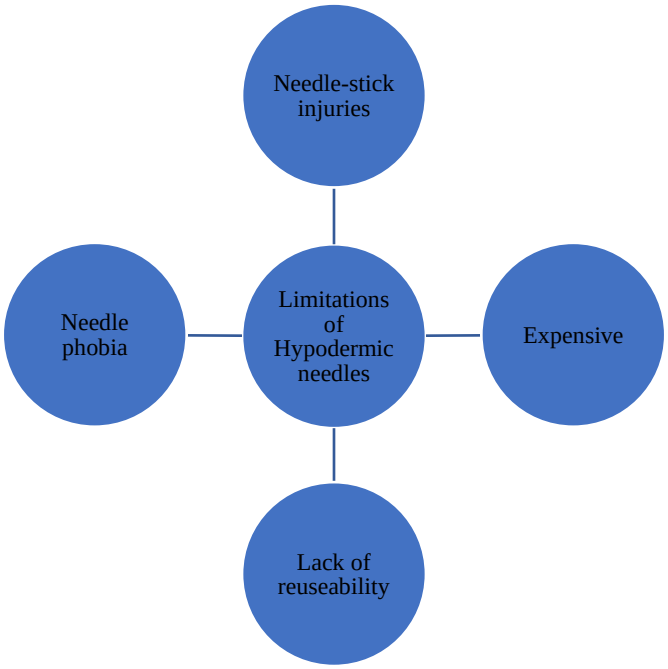

Figure 19

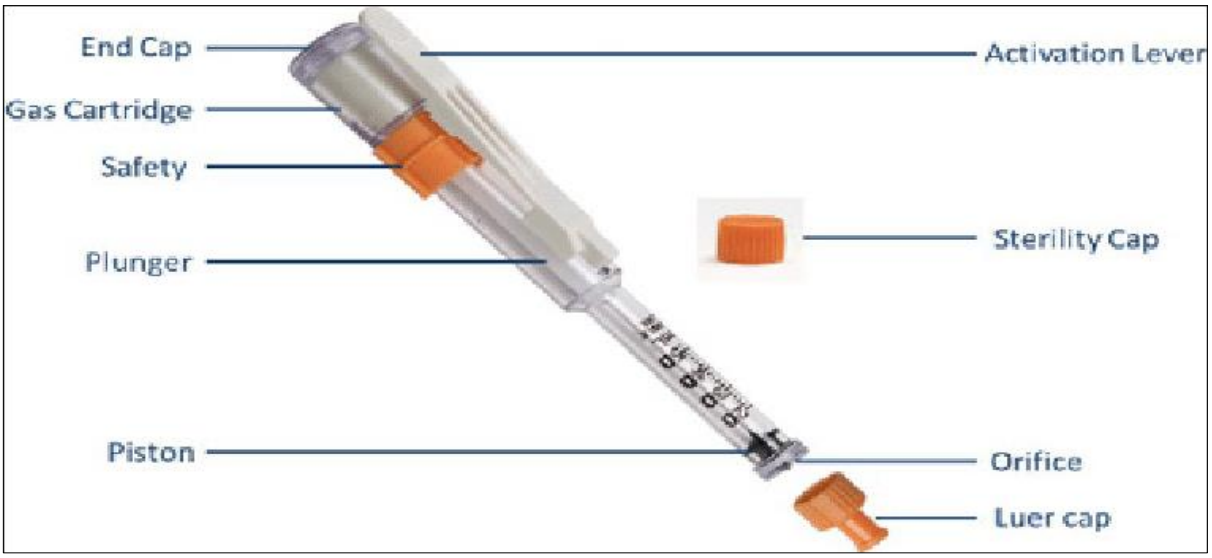

Figure 20

A needle less injector consists of three (3) main components:

C) Components of Needle Free Approach Device

Component 1.1 - Injection device:

It contains a drug and is built so that it can be dependent-administered. Plastic is used to construct the device. The device's stability is maintained throughout. It comes with a plastic needle-free syringe that has been infected.

Component 2.1 - Nozzle:

The nozzle acts as both a route for the medicine and a skin-contact surface. When the medicine is injected, the aperture in the nozzle dont allows the drug to penetrate the skin. The opening is usually 102m in diameter. The nozzlae firaes drug particles at a depth of 2.2 mm at a spaeed of 101 m/s. The most common orifice size is 0.129mm, which is about the same size as a 22-gauge needle. As a result, this injection is painfull; the patisent feels a tap of gas on the skin, similar to a finger flicking against the skin.

Component 3.1 - Pressure source:

It is critical for deliverring a medicine into the circculation via the blood with force. A mechanaical method of stored energy in a punching and releasing it by pressurised a pllunger to provide the required pressured can be used as the pressure source. It can also be a pressure storage method that helping pressed gas in gas caartridge as Carbon dioxide and nitrogen are the mostly commonly used gases in electronics. In portable units, pressurised steel air cartridges are frequent dont provided for access. Device design has an impact on the precision of drug distribution and the stress placed on the product. The devise must ensure that enough high pressure is generated to create skin puncture while not damaging the medication molecule. Like monoclonal antibodies, fragile medicinal molecules are vulnerable to destruction by high pressure. As a result, the design of devices may differ depending on the medicine for which they are intended.

The mechanism is shown in Figure

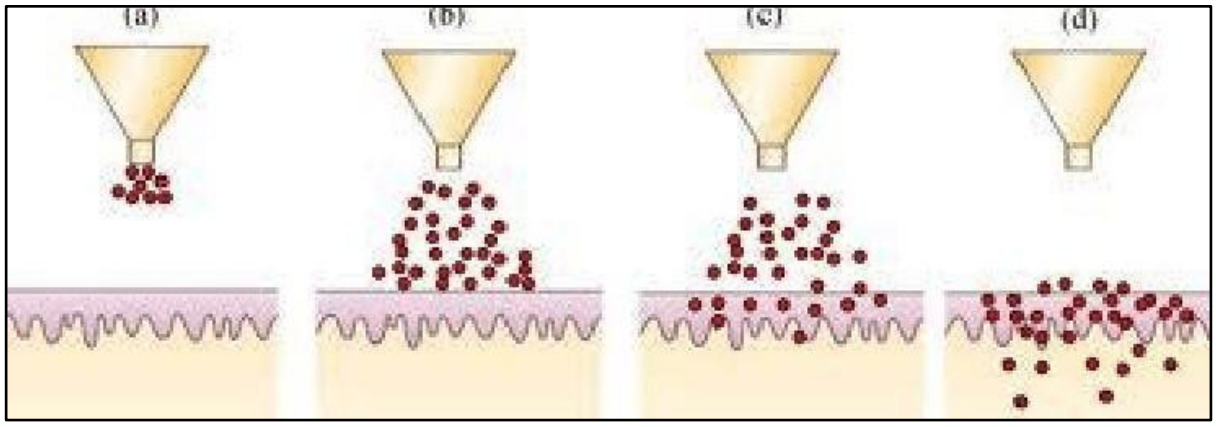

Figure 21 Figure for Mechanism of a powder injection

D) Mechanism

System Type 1 - Liquid injections

. Although the idea is the same as in powder injection, the powder injection devices are designed and operated differently. Gas or spring pistons, drug-loaded chambers, and nozzles are used in these systems. The orifice size of the nozzle is usually between 150 and 300m.

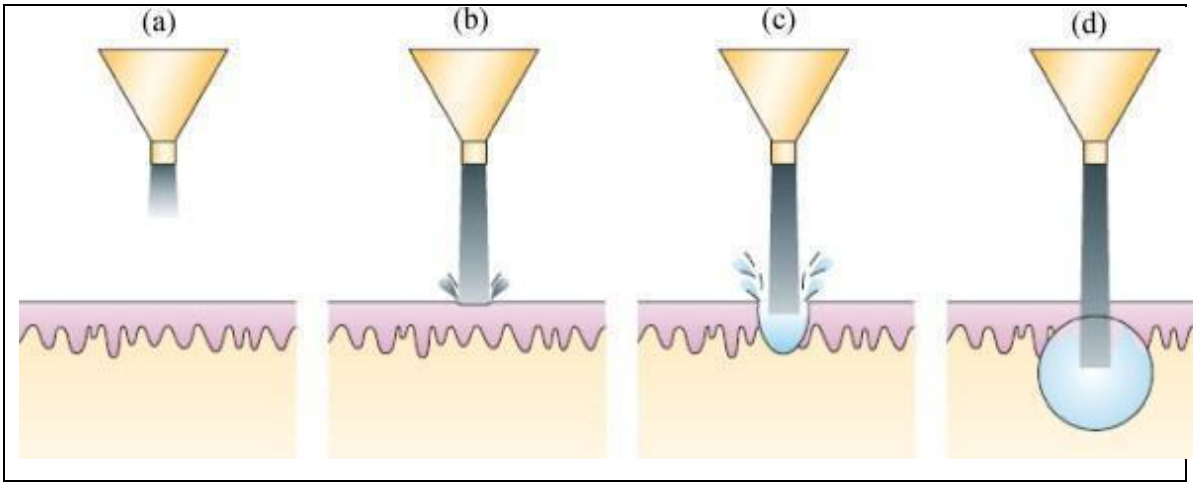

Figure 22 Figure for Mechanism of a liquid injection

System Type 2 - Depot or projectile injections

These systems are designed for administration of a drug into muscles. They create a store of drug into muscles that is released continuously over a desired time period.

E) Marketed formulation of needle free injection technology

The various marketed products include:-

(1) Biojector2000: needle-free technology works by forcing liquid medication via a huge opening held against the skin at a slow speed. The opening is only a fraction of the diameter of a human hair. With the use of a needle, an ultra-fine stream of low pressure fluid penetrates the skin. Bioject's technology is unique in that it can deliver injections at same depths and can handle a small range of injection volumes. The Biojector 2000, for example, can provide injections up to one ml in volume intramuscularly or subcutaneously.

(2) Vitajet3 : The Vitajet 2 is a needle-free injection method for delivering insulin that is simple to use and affordable. There is no need for maintenance or re-assembly with this technology. It comprises of sterile posable nozzles that may be replaced twice a week and are thus reusable, while still providing the inconvenience of a sterile disposable. The dosage and frequency of administration can be simply determined.

(3) Coolclick: It was created primarily for the delivery of human inhibitory hormone.

(4) Serojet: The SeroJet is a needle-free injectable method that delivers Serostim recombinant human growth hormone to adults suffering from HIV-related wasting. AIDS-associated wasting is a metabolic disorder in which HIV-positive persons gain weight. This could lead to an increase in morbidity and mortality if not managed.

F) Recent advances in needle free technology

1. **Biojector**

   It is the only FDA-approved intramuscular system. Because it uses double-use syringes for l injections,simple contamination is minimised. The Biojector 2000 has successfully provided over 10 million injections with no severe issues reported. In higher-risk situations, like as administering drugs to HIV or hepatitis patients, this approach has proven to be safe and effective.

2. **Vitajet 3**

   The device is made up of disposable nozzles that must be replaced twice a month. Insulin is delivered subcutaneously using this device. It was approved for commercialization by the FDA in 1996.

3. **Serojet**

   Vitajet technology is used in the Serojet gadget. The device is intended for subcutaneous administration of Serostim recombinant human growth hormone. This drug was approved for commercialization by the FDA in March 2001 for the treatment of AIDS-related wasting in adults.

   Mhi-500

   This device is used to administer insulin subcutaneously. The FDA approved the system in 1996, and it is now available for purchase throughout JAPAN. The device emits a tiny jet of insulin through the nozzle, reaching the subcutaneous layer's skin tissues.

4. **Iject**

   The device is intended for double-use, disposable administration via cutaneous or intermuscular injection. It's a second-generation gas powdered injection system from the Bioject Company. The trigger sleeve must be rotated 180 degrees to

activate the device. The injection is given by moving the trigger sleeve forward, with the nozzle against the injection site.

5. **Cool-click**

   This technique was created for the subcutaneous injection of Saen recombinant human inhibitory hormone. In June of 2002, the FDA gave its approval to the system.

6. **Recojet**

   Shrey Life Sciences has developed combinant human insulin, and the gadget is designed to distribute it.

7. **Intraject technology**

   The device resembles a pre-filled and disposable fountain pen. The apparatus is suited for the preparation of liquid proteins. The medicine is delivered in less than 60 milliseconds by pushing an actuator with compressed nitrogen.

8. **Biovalve's Mini-Ject technology**

   The device is easy to use, comes pre-filled, and is disposable. Large proteins, delicate antibodies, and vaccinations can all be delivered with this device. Intradermal, subcutaneous, and intramuscular delivery are possible.

9. **Antares Medi-Jector Vision technology**

   The insulin-delivery device was created with this in mind. It's reusable, spring-loaded, and can give a variety of doses.

auto and pen injectors

These spring-loaded syringes are used to administer a single dose. Because of its patient acceptance and safety profiles, auto injectors are very popular on the market. These injectors are promising because of a new design that includes a first pre-filled single-use device that includes a standard pre-filled doube-use device as well as a standard pre-filled syringe that needle insertion, drug administration, and needle cover before use. The needle tip is protected by this design. Such a design protects against unintentional fire.

Examples include:

• Anepens, Epipans,

• Rabeject, RebijectI for multiplee sclerosis.

Pen cartridges are used in pen injectors. A pattient's prescribed doce can be extracted from pen cartridfes using an insulin syringe and needle. These pan carrtridge used as multiplle doce vitals.

10. Madajet

In dentistry, this is a common injector. It operates by releasing local anaesthetic using pneumatic pressure. The medication formulation is injected into the skin at a depth of 4 to 5.5 mm below the epithelium. At the injection site, this stream creates a 5 to 6 mm diameter wheel. The device injects 0.1 cc of fluid every injection into the skin.

11. Bioject ® - Zetajet

A porteble injectorr and an auto-disebaling dispasable siringe are included in this system. It can be used both subcutaneously and intramuscularly. A volume range of 0.06 mL to 0.4 mL is injected by the system.

12. Injex needle free injections for infiltration anesthesia

The injection ampoule on this gadget has a 0.18 mm opening. The medication is discharged into the submucosa through this aperture at a dosed pressure. Local anaesthetic can be administered using the system. The ampoule must be positioned at a 90° angle on the associated gingiva exactly above the toth to be anaestetized. The maximum amount of llocal anaesthetic that used is 0.3 mL.

G) ***Advantages of needle-free injection over conventional dosage form***

1. Prevents skiin puncturre dangers and; does not causee bleding ; and has a little skin reaction.

2. Provides faster drugs delivary and more repeatability than invesive drug delivery methods, resulting in increased bioavailability as compared to invasive drug delivery systems.

3. Improved medication stablity duriing storege because it is administered as a dri powdar, which is especially important for watar-sensitdive pharmaceutical.

4. Prevents problems with reconstittution and shering effects.

5. The phobia of needles is no longer an issue.

6. With needle-free injections, self-administration is possible.

7. It boosts the immune system's reaction to immunizations. Flu, tetenus, typhoid, diphtheria,, and hepaetitis b vaccsines can all be administered without the use of nidle.

8. Bio-equivalence has been proven, allowing generic medicine proteins to be developed.

9. Increased medication dosages produce a strong dose response.

H) *Disadvantages of needle-free injection over conventional dosage form*

1. The method is time-consuming and costly.

2. There is no such thing as a one-size-fits-all system.

3. Personnell trainings and maintenanse are required.

4. It is not suitablee for intravenous administration.

I) Future prospects

Needles less liquid jet injection have revolutionised the delivery of drugs and vaccines. They made history as the first larrge-scale needle-frree meethod for maccromolecule distribution and as a major component of mass immunisation programmes. DCJI (direct control jet injector) are a popular alternative to injector. They anxiety and provide a preferred way of delivery for many needle-phobic people. They also eliminate problems with needles, such as punctures and sharps disposal. When compared to otherr needlee-

freee options such as patchees, sprrays, and pillss, jet injectors have the advantage of being able to use existing needle-based injection formulations. Reduces developments and clinical trial times result in significant cost reductions. Despite more than 51 year of clinical uses, needle-free liquid jet injectors have yet to attain their full potential. This is due to a number of variables, including the possibility of pain, discomfort, and local responses, as well as the inconveniencse of usea compareds to injection and the expense.

The cause of periodic pain is unknown. It's likely that variations in a jet'sa penetration depath are linked to occasional pain and bleeding. Jets that penetrate deep into the dermal and subdermal layers may interact with nerves and blood vessels. Direct interactionas with nervesa or bloods vesssels could be avoided by limiting jet penetration to the superficial layers of skin. Variability in pain could also be linked to the lateral density of neurons and blood vessels. In that instance, using lower nozzle diameters may be beneficial. Currently, the jet parameters employed in various commercial jet injectors differ just slightly. The majority employ nozzle diameters between 150 and 300 m and velocities between 100 and 201 n s–1. More research is needed to investigate jet performance beyond this range. Smaller nozzle diameters need to be given special consideration. More study is needed to answer a number of other fundamental problems. The effects of jets on skin at a cellular level, for example, are unknown. This concern is especially pertinent in view of potential jet injection applications in genetic immunisation. It's likely that variations in a jet's peneetration depth are linked to occasional pain and bleeding. Jets that penetrate deep into the dermal and subdermal layers may interact with nerves and blood vessels.

8. CHALLENGES IN TDDS

Transdermal drug delivery is both interesting and challenging. Various transdermal delivery strategies are now available. However, the transdermal market is currently limited to only a few drugs. The ability to overcome the constraints of medicine permeability and skin irritation is required for further developments in transdermal

administration. Thus, the conventional mode of drug delivery would be expanded if new techniques to improve skin permeability and measures to decrease skin irritation are to be discovered. Since it pace into research is exponential , it is assumed to have a very bright future in near future.

Right now TDDS is into preliminary stage where only limited scoped medication are being able to administered through passive diffusion and majority of TDDS products are based on this. Where as certain sophisticated chemical and physical methods have been utilized to disperse pharmaceutical molecules that cannot be supplied by passive diffusion as science and engineering have developed. These are part of the second generation of transdermal products, which try to disturb the stratum corneum, the skin's outer layer, in a reversible way or other impulse alternative which can be used for delivery , Like in iontophoretic delivery system to generate and sell lidocaine (a charged molecule). Microneedles and electroporation are two of the third generation of delivery systems' techniques of delivering macromolecules. Rather of altering the medicine molecule itself, the third generation of devices targets the stratum corneum.

As the epidermal layer being a barrier for drugs which only lets in a selective drug and that too in specific quantity only . The issue arises when macromolecules are to be delivered like insulin. Skin permeability are need to be managed to get desired efficiency. Where it is depended on drugs nature and skin permeability.

9. FUTURE PROSPECTS OF TDDS

Expanding the use of innovative permeability enhancement technologies to allow drug molecule to pass through transdermal route. The rate of therapeutic agent diffusion over skin can be significantly increased with physical augmentation techniques. It is predicted that the products of transdermal prodrug will soon be commercialized. Some nonconventional prodrugs may be applied with some drugs not only achieve therapeutic levels, but also reduce skin issues.

The prevalence and intensity of skin irritation reactions will decrease as physical permeation improvement technologies and new breakthroughs in topical pharmaceutical formulations. Breakthroughs in the creation of chemical permeation enhancer analogues are being so amazingly developed that they have readily removed skin irritation as well as enhanced permeability.

10.CONCLUSION

Various formulations are working to improve the bioavailability of low-absorption medications by using simple modes of administration that allow large dosages to be given over time. As a result, TDDS technology is rapidly gaining traction in the pharmaceutical industry, and it has successfully captured an important market share in biomedical applications as a formulation system that can increase drug administration via topical channels. This has been associated with the advantages of the transdermal method, such as the lack of first-pass metabolism effects on the liver, improved patient compliance, consistent release profiles, and decreased pill load. In order to make TDDS more effective various physical and chemical methods are utilised which majorly solves certain problems and are very patient friendly and convenient . These methods have really enhanced the bioavailability. These made TDDS a great option for drug administration. However, only lipophilic, low molecular weight strong medicines can be delivered through skin due to this barrier created by human skin which obstructs permeation. It is found that the applicability of solution or suspension are limited. Keeping system's functionality and usability in mind transdermal devices are to be designed.

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