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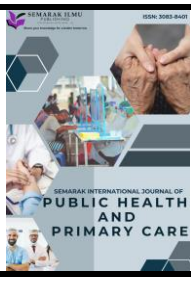

Microneedle and Their Current Progress in Vaccine and Protein Delivery: A Review

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ABSTRACT

Microneedles (MNs) allow drugs to directly enter the systemic circulation, which allows better bioavailability, rapid absorption and efficacy over the conventional dosage forms. However, this passage of drugs through the transdermal route is restrict due to the presence of the stratum corneum, the upper skin of the human body. Microneedle is known for delivering a wide of drugs such as molecules over around 500 Da with high lipophilicity as the conventional dosage forms like gels and patches cannot easily cross the stratum corneum. This limitation of traditional transdermal drug delivery is addressed by microneedles. Moreover, microneedles should be selected instead of traditional injections due to their lower skin irritation, less site of pain and less discomfort. This review aims to address the concerns that arise when the study of microneedles. Explore the microneedles usage in different classifications of authorized microneedles, materials use and current trend aspects of microneedles and advance study on recent medication delivery using microneedles and in vaccine delivery. The study will attract readers from the field of pharmaceutical industries, academicians and material scientists.

1. Introduction

1.1 Drug Delivery Systems

The drug delivery system mainly includes carrier selection, targeted delivery and applications like oral delivery, dermal delivery, etc. Different carriers need to have good biocompatibility and stability. Specific targets are receptors, enzymes, in vivo electrolyte balance systems and ion channel regulation which can be know from the molecule, cell, tissue and biomarkers.

Drug delivery systems describe technologies that carry drugs into or throughout the body. These technologies include the method of delivery, such as a pill that you swallow or a vaccine that is injected. Drug delivery systems can also describe the way that drugs are 'packaged'— like a micelle or a nanoparticle—that protects the drug from degradation and allows it to travel wherever it needs to go in the body. The field of drug delivery has advanced dramatically in the past few decades and

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even greater innovations are anticipated in the coming years. Biomedical engineers have contributed substantially to our understanding of the physiological barriers to efficient drug delivery and have also contributed to the development of several new modes of drug delivery that have entered clinical practice. Yet, with all of this progress, many disease treatments still have unacceptable side effects. Side effects occur because drugs interact with healthy organs or tissues and this can limit our ability to treat many diseases such as cancer, neurodegenerative diseases and infectious diseases. Continuing advances in this space will help to facilitate the targeted delivery of drugs while also mitigating their side effects [1].

There are three main categories of vaccines: prevention, treatment and diagnosis. In our lives, the vaccine delivery drug process is widely used in hospitals for different age groups people ranging from paediatrics to elderly people. Preventive biological products: bacterial vaccines, viral vaccines, etc. Therapeutic biological products: antitoxins and antisera, blood products, biotechnology products, etc.

Overall, for an extended period of cancer treatment, cancer vaccines may be the next ultimate combination partner, providing a proposal that is effortlessly combined with existing therapies, with negligible toxicity and a superior safety profile [2].

Vaccines nowadays for instance world widely used in vaccines, for public health prevention particularly from at risk of the disease, another vaccine for diseases such as cancer, respiratory syncytial virus and flu vaccines, those vaccines that have contributed to a significant reduction of diseases.

Microneedles are yet to fully operational in vaccine delivery in preclinical and human trials. Moreover, usage of dissolving or hollow, etc, microneedles take time to consider for common use in hospitals, industrial and health care occasions, microneedles are costly and actual use is not practical in the pharmaceutical industrial, but expensive research has been done for microneedles. The clinical study also on the progress for this to get appropriate outcomes to process. Now here is the study on transdermal drug delivery system microneedles that promote the exploration of different types of microneedles.

Respiratory syncytial virus or RSV is a highly contagious virus that is easily spread from person to person, most often through coughing or sneezing and causes infections of the lungs and breathing passages in individuals of all age groups. It typically causes mild, cold-like symptoms in most people. RSV infection is especially common in children and most young children have been infected with RSV by the time they are two years old. Some people, particularly infants and older adults, are more likely to develop severe RSV disease and need hospitalization [3]. In some typically diseases can be more strong evidence for the role in transdermal drug delivery. U.S. Food and Drug Administration indicates the vaccine use in certain diseases.

1.2 Transdermal Drug Delivery System

Transdermal drug delivery systems are dosage forms that absorb drugs into the body through the skin to exert systemic effects. When use to treat disease, different types of microneedles, namely hollow MNs, dissolving MNs, solid MNs, etc. Are used for the appropriate application. The percutaneous drug delivery system involves the absorption of drugs through the skin and into the systemic circulation through the capillaries, “carrying” them through the body. Table 1 presents the components of the capacity for transdermal drug delivery.

Table 1
Components of the capacity for transdermal drug delivery

Type	Irritation	Bioavailability	Site of Action	Storage
Microneedles		√	√	√
Traditional Injection	√	√	√	
Patch				
Other				

Transdermal drug delivery directly acts on the site, avoids the first pass effect of the liver and gastrointestinal discomfort, has no side effects of the drug on the stomach and reduce the times of absorption, when side effects are there, the administration can be found in time and intervention can be give, a constant blood drug concentration can be maintained, etc. Transdermal drug delivery is the delivery of drugs across the skin and into the systemic circulation act to the relative accessibility of the skin, which is altogether different from topical drug delivery which can only target the local effect areas. A thorough understanding of the physicochemical structure and properties of the skin is immensely important to deliver therapeutic agents through the human skin for systemic and desired effects. Transdermal delivery advantages are over other forms of injectables and oral routes by increase patient compliance and avoiding first-pass metabolism.

2. Microneedles

Transdermal drug delivery system (TDDS) refers to a class of preparations in which drugs are absorbed through the skin through capillaries into the systemic circulation. Microneedles (MNs) are a physical method to promote the transdermal absorption of drugs.

The MN delivery system, which consists of an array of submillimetre-sized needles (up to 1500 μm in length) attached to a base support, has been shown to be able to penetrate into the viable epidermis of the skin, bypassing the stratum corneum (SC), the outermost layer of the skin. In this way, the delivery of pharmaceutical ingredients becomes possible in a pain-free manner, as the MN delivery system avoids interfering with the dermal layer, which is where all nerve fibres and blood vessels are mainly located. The system has been proven as a valuable technique in delivering drug molecules with higher masses (over 500 Da) and various polarities [4].

Microneedles can pass through the skin epidermis and can be divided into hollow, solid, dissolving, coated, etc, which is suitable for the administration of biotechnology drugs such as nucleic acids proteins and vaccines.

The therapeutic ingredients include small molecules; biomacromolecules (proteins, hormones, peptides); vaccines for SARS, MERS and COVID-19; and genes [4].

Microneedles have a certain size, which causes mild physical damage to the skin stratum corneum through the puncture effect of microneedles. Through the action of microneedles, a position with a diameter of about a micron is formed on the skin stratum corneum and can exist when removed. The bioavailability of transdermal drug delivery preparations is relatively high.

2.1 Microneedles and Usage

Microneedles can be divided into namely hollow and solid microneedles and others. Different types and materials for microneedles, with different insertion sizes and shapes: a variety of materials together with the different types of microneedles used for each type of microneedle have their characteristics, advantages, drawbacks, applications, studies to use in diabetes, oncology, hepatitis

diseases and know other diseases and conditions. Microneedles are a method of drug delivery that greatly reduces pain when inserted into the skin compared to ordinary and traditional ones.

Experts from academia, industry and regulatory organisations are collaborating to help MNs to advance into safe and effective clinical usage provided that the shortcomings associated with these systems are promptly and rationally addressed [4].

In the field of drug delivery such as for diabetes treatment, cancer treatment, vaccination, etc, conduct the topic to determine whether the patient has a health outcome toward the diagnosis and treatment, the validity and reliability of the results. Table 2 shows the information mainly about the microneedle types and their suitable way to be used. Challenges occur when a study on the way to deliver the medication. However, due to the serval types and novel microneedles are undergoing by progress in usage so an attempt to address the challenges such as safety, compatibility, biodegradability, fabrication, stability and regulatory. Limitations on different types of microneedles are mainly based on safety for the skin decreased irritation and allergy. Delivery material used and the cost of the fabrication, each of the points can contribute to the medication effectively to the site of action. As safety and effectiveness are the standards for the medication delivered to humans, to consider every aspect of regular microneedle use, especially for clinical application. Another limitation of the microneedle is the patient acceptability and awareness about the usage. Table 3 outlines the different types of microneedles and their functions.

Table 2
Highlights some limitations with the type of microneedles

Microneedle types	Site of Action	Function	Challenge and Limitation
Solid Microneedles	Epidermis	The solid microneedles are insert into the skin to the site, then the solid microneedles are removed, the drug is applied or applied with a drug patch to the site and the drug is diffuse through the pores to deliver the specific drug.	Challenge：Safety. Limitations: • Needle may breakoff within the skin. • Silicon MN involved complicated fabrication [5].
Dissolvable Microneedles	Epidermis	It is about the use of biodegradable polymers, etc, the drug attaches to the microneedles, when the drug is administered, the needle dissolves after insert perhaps with the skin interstitial fluid and the drug is release locally.	Challenge: Compatibility, Biodegradability. Limitations: • Limited drug loading capacity. • Not suited for active macromolecules encapsulation [5].

Table 3
Microneedle types and their function

Microneedle types	Site of Action	Function	Challenge and Limitation
Hollow Microneedles	Epidermis	After the hollow microneedles are insert into the skin, the drug is transport into the skin through the internal pore under the drive of pressure and the drug is continuously delivered intermittently and the delivery speed can be adjusted with the dosage.	Challenge: Fabrication. Limitations: • Fabrication method is difficult and costly. • Clogging of skin tissues during insertion. • Less mechanical strength. • Larger tip diameter leads to poor insertion [5].
Coated Microneedles	Epidermis	The drug perhaps is attached to the surface of the microneedles to form a site, the drug attach to the microneedles after the micro acupuncture is inserts into the skin will dissolve and releases from the microneedle into the skin.	Challenge: Compatibility, Biocompatibility. Limitations: • Small amount of drug can be coated (suitable for potent drugs). • More coating can compromise the sharpness of the needle and therefore the insertion [5].
Hydrogel Forming Microneedles	Epidermis	Hydrogel forming and some novel types of microneedles that still explore in a specific situation with polymeric and certain nature of medication use for the patient. Moreover, perhaps the hydrogel form is more or less similar to the dissolving type of microneedles it is prepare from a hydrogel polymerize matrix.	Challenge: Stability, Regulatory Approval. Limitations: • Poor physical stability and mechanical strength [5].

3. Different Types of Microneedles

When drugs are absorbed into the body, as both internal and external organs part of the body, prevent functionality leads to drugs not being effective or difficult to reach the therapeutic demand, first and foremost assume that at a certain level effective in the body, remains some pattern of microneedles which are more appropriate. A certain range of points approach data estimation: permeation coefficient and lag time, which are important because it is in the role of baseline before application to use. Promote transdermal absorption of drugs by physical methods, penetration enhancer technology effectively expands the range of drugs that can be used for transdermal delivery, especially protein and small molecules and the penetration promotion method can precisely control the transdermal absorption. Microneedles are enough to penetrate the skin and types can be divided into solid and hollow, etc. Solid microneedles form micron-sized cavities on the surface of the skin, remove the microneedles, apply the drug to the pierce site and allow the drug to enter through. Hollow microneedle when it is into the skin is driven by pressure to deliver drugs through internal.

Hollow microneedles have a hollow bore in the centre of the needle that allows for easy insertion and removal [5]. Hollow microneedles have the ability to modify pressure and hence flow rate, allowing for a rapid bolus injection, a gradual infusion or a variable delivery rate [5].

In coated microneedles the drug is likely attached to the surface of the microneedle using infiltration, coating or drug loading outside the needle, when the drug is administered after the micro acupuncture is inserted into the skin, the drug dissolves in the skin into the intercellular fluid and is

delivered into the body. Coated microneedles are microneedles that have been coated with a drug-containing dispersion before being used [5].

Dissolving microneedles perhaps is that after penetrating the skin, the needle made of degradable materials gradually degrades in the microenvironment, the drug is released synchronously and the drug molecules pass through the barrier and are absorbed into the body through the tissue.

Hydrogel forms perhaps when the hydrogel microneedle is administered, it is through the interstitial fluid and the drug is delivered into the human body through the micropores of hydrogel under the infiltration and diffusion of the interstitial fluid.

3.1 Microneedle and Applications

The types of microneedles and the materials used in different types can combine with more aspects to explain namely in certain types of it. For the choice of drugs, the small drug dose and the daily dose should be in a certain range and the pharmacological effect be strong. The relative molecular weight of the drug, melting point, molecular structure, etc, which relates directly to the point should be in a certain value.

The biological half-life of the drug is short and average in general, with less irritation to the skin and less allergic reaction. Types of microneedles together with certain concentrations of the drug, cumulative percutaneous transmission of drugs and time to use and effect. Adjunct materials and properties of transdermal drug delivery for their use. Types of microneedles and associated patterns of drug delivery and their applications in either therapy or diagnosis. It is perhaps also found to be used in other fields, starting from the point of view, which is more reliable, safety and effective.

It is about to study and explore. These include drug delivery, vaccine delivery, disease diagnostic and cosmetics application [6].

3.2 Materials Used in Microneedles

Various types of microneedles. Their uses extend from in vitro to in vivo applications. The microneedle uses polymers namely biodegradable and nonbiodegradable.

There are methods to fabricate microneedles using biodegradable polymers, etc, making medications better absorbed into the skin then to the effect sites. Different types and materials of microneedles with different insertion sizes, shapes and materials: biodegradable, non-degradable, etc. Compared to others, biodegradables have advantages that can be weighed.

3.3 The Microneedles Form with the Usage of Polymers

Microneedles have been fabricated from various materials: in different shapes and sizes for a wide range of applications. Biodegradable one poly lactic-co-glycolic acid (PLGA), etc.

As non-toxic, biodegradable, biocompatible materials, the polymeric microneedles have a great significance in terms of delivering therapeutic drug molecules through the skin [7].

As a comparable drug delivery mode, as well as the materials use for microneedles, further exploration depends on the acceptability of the microneedles form of the specific one to standardize use with the eco-friendly consideration. Applicability for microneedles in either therapy or diagnostics.

4. Hollow Microneedle

Hollow microneedles (Figure 1) compared to those taken orally can avoid the first pass effect and gastrointestinal discomfort. Moreover, compared to through injections sufficient bioavailability, less pain, fast and more or fewer factors affect compliance and adherence.

The hollow microneedle array has the advantages of the syringe and transdermal drug delivery patch, which is suitable for liquid and certain demands of dosage and easy to monitor, such as nucleic acids and vaccines.

Relatively large quantities of therapeutic ingredients may be supplied into the skin with the “poke and flow” approach, which, by using hollow MNs, could potentially overcome the dose limitation associated with solid MNs. With hollow MNs, it is technically possible to control the flow and dosing by diffusion or pressure or electronically (e.g., using a pump) and to integrate them into lab-on-chip devices. Similarly, bio-macromolecules, including proteins, vaccines, mRNA and diagnostic agents, can be delivered via hollow MNs [4].

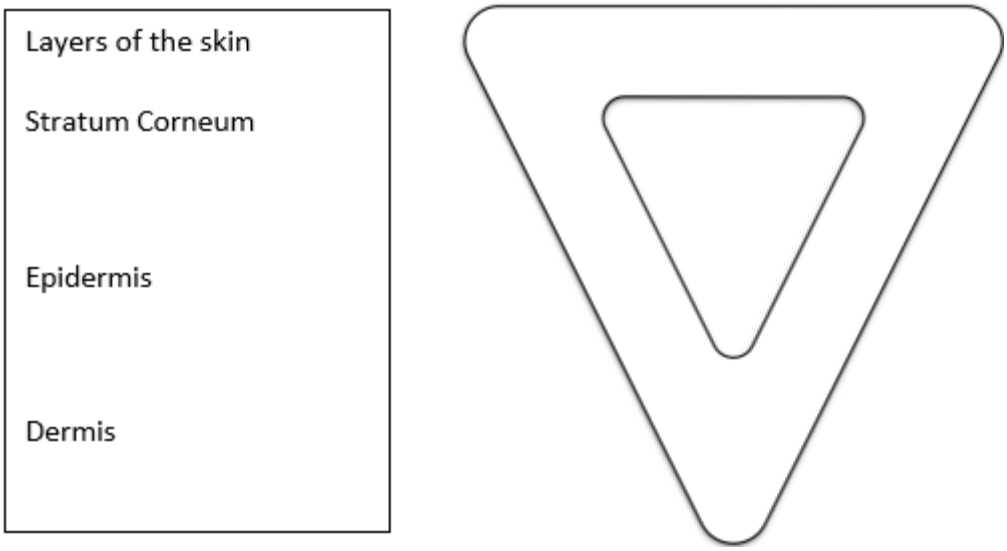

Fig. 1. Hollow microneedle

4.1 Hollow Microneedle Characteristic

It is shown that the drug or vaccine can be absorbed into the stratum corneum's even deeper site which is the epidermis part which also depends on the length of the microneedles. When it comes to managing drug dosage, delivering the drug when collecting the biomarker from the patient could be easier. Compared to the syringe, less painful and more convenient to use and store, the sites of the skin that can be applied for the therapy or diagnosis, drug can be visible not only on any difference between before and after the use of medication but also on day-by-day improvements.

Nonetheless, the construction of hollow MNs is relatively complicated and suffers from clogging, drug leakage, structural fragility and the requirement of a larger tip diameter, which leads to poor insertion [4].

4.2 Pattern of Hollow Microneedles Drug Delivery

Hollow MNs currently used for drug delivery, (insulin delivery, etc.) and vaccine delivery, etc. After the hollow needle tip is inserted into the skin, the drug enters the body under the pressure

driven by the part of skin tissue to achieve drug delivery with improved patient comfort and safety of use.

4.3 Basic Microneedles Shape and Material

The geometry depends more or less on being able to penetrate the stratum corneum and not break or deform easily because it will lead to skin damage and infection.

The materials selected for preparation, hollow microneedles can be divided into silicon, polymers, etc. The way for drugs to be absorbed is that liquid can flow into the skin via the hole in the tip of hollow microneedles driven by the pressure microneedles are composed of micron level size needles to a base in the form of an array.

4.4 Hollow Microneedles Array

Figure 2 shows a hollow microneedle array. Microneedles are composed of micron-level size needles to a base in the form of an array. The length of microneedles can be controllable to penetrate the stratum corneum and form sites in the epidermis to affect the dermis less and without hurting nerves or blood vessels.

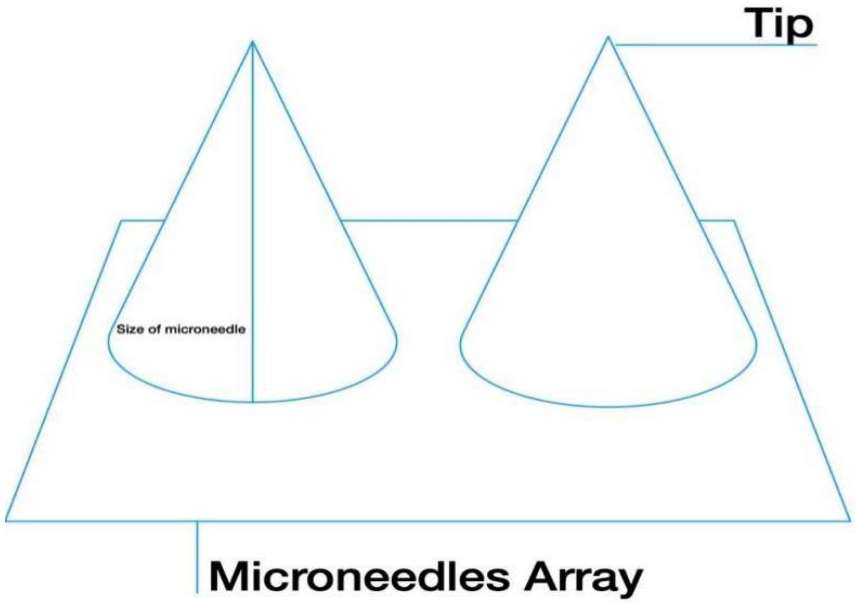

Fig. 2. Hollow microneedles array

4.5 Microneedle in Protein Delivery

The chemical structure of insulin consists of 51 amino acids, divided into two peptide chains: the A chain (21 amino acids) and the B chain (30 amino acids). For medication delivery purposes, the binding protein among the medication molecular and protein.

Others: Nucleic acid, polypeptide. Nowadays microneedles ensure safety and a sense of more comfort with fast effects. The variety of materials used is not difficult to obtain but seeks for the enhancement. Microneedle array's insert length typically has flexibility. Quality requirements together with data process and pharmacokinetic evaluation of transdermal drug delivery are also important.

Protein denaturation, drug absorption efficiency and cellular permeability related to molecular size can all be reduced during dosage and storage, resulting in reduced therapeutic efficacy. Microneedle research is being carried out in order to improve the efficiency with which protein medicines are delivered [5].

5. Purpose of Microneedles

Microneedles rely on their micron-level sharp tips to pierce the skin, form a certain depth of site, to facilitate drug molecules more easily through the skin or directly to achieve drug insert, painless and efficient transdermal drug delivery, penetration and absorption purposes. The microneedles of medication delivery depend on the situation of different areas. How can deliver the drug is mainly because the skin to absorb into the effect site and delivery, it is possible through microneedles effect all bodies or target sites which means there must be “carrying” and “effective” when microneedles are apply to deliver the drugs. Microneedles and drug delivery system, mean the purpose of microneedles can be knowing clearly. The mechanism of action of drugs is usually manifest in the specific between drugs and sites and the process of producing therapeutic effects.

When using the medication on the human skin, whereby transdermal drug delivery to deliver the medication, there are moment effects that start from the site where the medication.

5.1 Hollow Microneedles

Figure 3 depicts a hollow microneedle. After the hollow microneedles are inserted into the skin, the drug is transported into the skin through the internal pore under the drive of pressure and the drug is continuously delivery intermittently and the delivery speed perhaps can be adjusted together with the dosage.

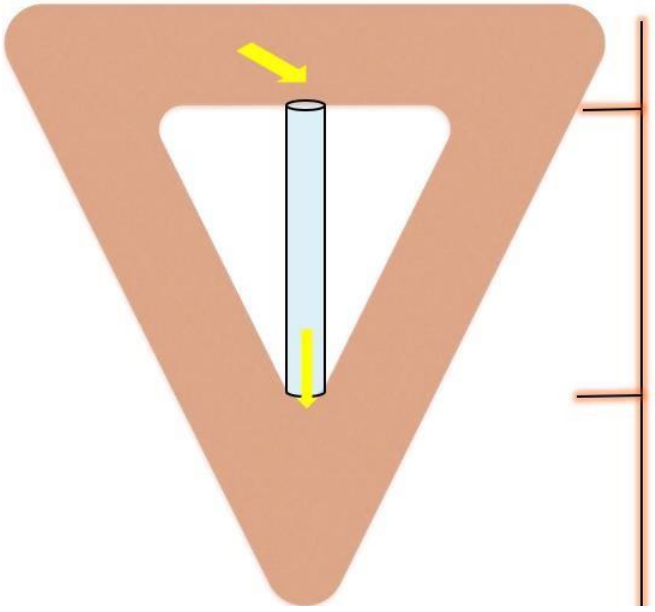

Fig. 3. Hollow microneedle

5.2 Dissolvable Microneedles

Figure 4 illustrates a dissolvable microneedle. It is about the use of biodegradable polymers, etc, the drug attaches to the microneedles and when the drug is administered to the site, the needle dissolves after insertion perhaps with the skin interstitial fluid and the drug is released locally.

The “poke and dissolve” approach, in which water-soluble therapeutic agents are carried into the skin, uses mostly biocompatible/biodegradable and low-cost polymers. Hyaluronic acid, sucrose, polylactic/glycolic acid (PLA/PGA) and chitosan are among the polymers often used for the construction of dissolvable MNs (dMNs) [4].

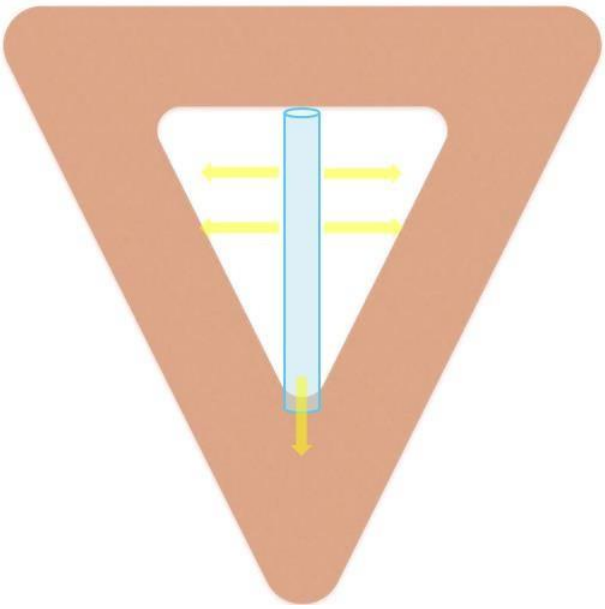

Fig. 4. Dissolvable microneedle

5.3 Solid Microneedles

Figure 5 shows a solid microneedle. The solid microneedles are inserted into the skin to form the site, then the solid microneedles are removed, the drug perhaps is applied or applied with a drug patch to the site and the drug is diffused through the pores to deliver the specific medication.

The pore-performing pre-treatment of the “poke and patch” approach involves the application of a solid MN patch to create small holes in the skin, followed by a conventional drug application on the surface of the skin. The first reported fabrication of solid MNs was based on silicon to deliver calcein through excised human skin in vitro. Cost, fragility, biocompatibility and the complex manufacturing process have steered researchers to other materials, including metals, ceramics and polymers, in order to achieve better outcomes. Although the production of solid MNs is technically simple—no loading or coating is required—the two-step administration procedures and the no exact dosing with drug reformulations requirement are the main limitations of solid MNs, along with safety matters. Using solid MNs for the delivery of proteins, hormones and vaccines have been reviewed in detail elsewhere [4].

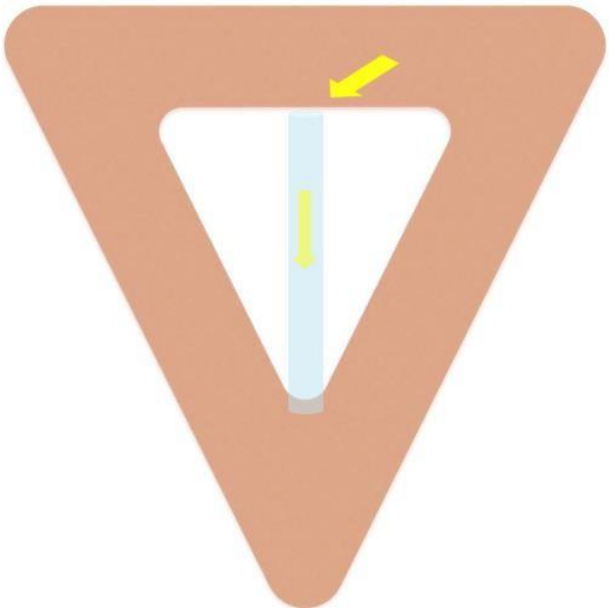

Fig. 5. Solid microneedle

5.4 Coated Microneedles

Figure 6 illustrates a coated microneedle. The drug perhaps attaches to the surface of the microneedles to form a site, the drug attaches to the microneedles after the micro acupuncture is inserted into the skin will dissolve and release from the microneedle into the skin.

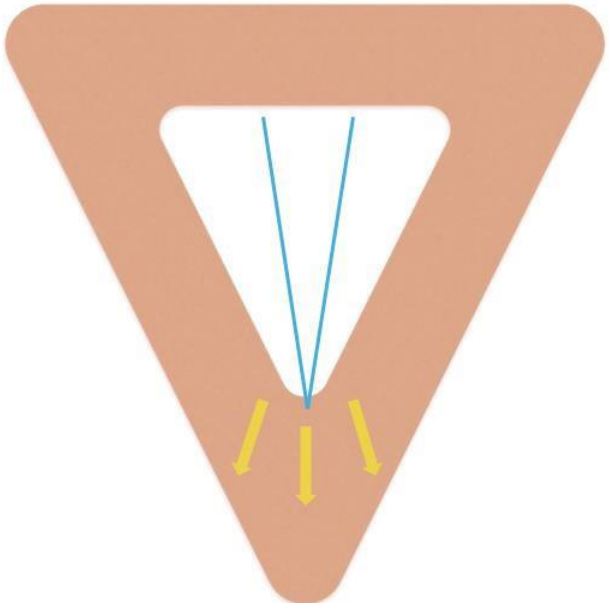

Fig. 6. Coated microneedle

5.5 Hydrogel Forming and Some Novel Types of Microneedles

With the polymeric and certain nature of medication use for the patient. Moreover, perhaps the hydrogel form is more or less similar to the dissolving type of microneedles it is prepared from a hydrogel-polymerized matrix. However, perhaps for further explore.

Fine-tuning of the delivery time is possible by adjusting the polymer decomposition from minutes to days. Nonetheless, their low strength and limited drug doses are among the limitations of hydrogel-forming MNs [4]. Figure 7 represents a complex microneedle system.

Fig. 7. Complex

5.6 Microneedles and the Route

Microneedles and the preparation techniques when necessary to make it more flexible in shape, easy to use, more acceptable for people and patients and fast to apply and use. To assess based on stratum corneum: percutaneous absorption of drugs perhaps can be divided into the appendageal route and the transepidermal route, based on the route: transepidermal route, appendageal route, transcellular route and intercellular route can be clearer. Area and factors include site, absorption rate and systemic circulation.

5.7 New Technology and New Dosage of Pharmaceutical Preparation

The transdermal drug delivery system developing in the United States and some new technologies are also derived from the countries that contribute original technology. Either the local which has excellent medical facilities institution or Germany has been able to produce the technology. Eg: The microneedle device Macroflux, after the administration of small protein through Macroflux, the blood concentration can reach the peak time and the bioavailability is high. One of the technologies is the 3D printing technology.

Moreover, categories, design, preparation techniques, etc, are important to the microneedles that can be use fast, widely and easily. Metals, silicon, polymers, etc, perhaps are essential because they contribute to the development of the transdermal drug delivery system. The application of microneedles, routes, mechanisms and effects can be found not only through properties but also through the process of use.

5.8 Nucleic Acid and Protein Delivery

Nucleic acid drugs the drugs are a variety of oligoribonucleotides (RNA) or oligodeoxyribonucleotides (DNA) with different functions, mainly at the gene level. It exists in almost most of the organisms.

Polypeptide perhaps is a class of compounds formed by the connection of multiple amino acids through peptide bonds, usually composed of several amino acid molecules, the connection way is the same as protein and the relative molecular weight is less than 10000 units. Polypeptides are commonly found in organisms. The polypeptides widely participate in and regulate the functional activities of various systems organs, tissues and cells in the body.

Specifically, the disease and conditions can be applied to use the microneedles that can be consider. The ability of drugs to pass through the skin perhaps can also be improved with the help of micron or nano drug carriers, liposomes. Purposes of microneedles over the skin with certain types, diseases situations and certain medications used. The carrier and effects play an important role in the process.

The effectiveness of MNs has been demonstrated in several clinical trials, but there have still been far more preclinical studies [4].

It is believed that, in time, microneedle-based technology will lead to improved illness prevention, diagnosis and control, as well as an increase in the health-related quality of life of patients globally [4]. Therefore, there is the study on the relevant topic to promote the desired outcome.

5.9 Vaccine Delivery through Transdermal Drug Delivery

Vaccines work through the body's system to reduce the risk of disease. Vaccines recognize viruses or bacteria and produce antibodies. Nowadays until bacteria or viruses reappear, the immune system can play a role in it and no longer gets the same disease. Still can make an effort to know about that treatment via vaccine delivery together with transdermal drug delivery.

Currently, cancer is a tricky disease worldwide, there are serval treatments and trends for cancer treatment.

In cancer development and progression, the significant role of antitumour immunity has been verified by fundamental and experimental research on the tumour microenvironment, inclusive of cancerous, stromal and immune cells [2].

5.10 Recent Examples of Vaccine Delivery using Microneedle

Vaccines are biological products in this category that are made by biological techniques that use microorganisms, cells, animal or human tissues, etc, start materials for the prevention, treatment and diagnosis of human diseases. The types of biological products are divided into vaccines, antitoxins and antiserum drugs, blood products, diagnostic products, etc. Whereas microneedles already have certain advantages in certain aspects, the recent explanations illustrate in Table 4 the superior nature of microneedles in delivering vaccines.

Table 4
Recent studies involve microneedles with vaccines

Microneedle type	Vaccine	Test animal used and test	Polymer used/microneedle material	Outcome	Reference
Two Compartmental Microneedle Array (CMA)	Influenza vaccines for B/Yamagata (B-Y) and B/Victoria (BV)	Mice and IM immunization	Polylactic acid (PLA)	CMA showed comparable efficacy with IM administration of the combination vaccine.	[8]
Dissolvable Microneedles	Bordetella Pertussis (PT) Subunit Vaccine	Mice and Immunological Evaluation	Poly (vinyl alcohol)	PT vaccine MNs successfully embedded into the mouse dermis to a depth of approximately 330 µm. PT vaccine MNs could elicit immune responses through multiple pathways, especially of Th1 and Th17 pathways .	[9]
Microneedle Patch	Measles Vaccine	Immunize cotton rats	Stainless steel microneedles	Measles vaccine can be stabilized on microneedles and that vaccine efficiently reconstitutes *in-vivo* to generate a neutralizing antibody response equivalent to that generated by subcutaneous injection.	[10]
Dissolving Microneedles	Zika virus strain PRVABC59/Zika Vaccine	Male Swiss Webster mice	Poly (D,L-lactidecoglycolide) 75:25 (PLGA)	The vaccine MPs-loaded dissolving MNs with adjuvants induced significant IgG, IgG1 and IgG2a Titers in immunized mice compared to the untreated control group	[11]
Dissolving MN	Microparticulate of vaccine (spike glycoprotein (GP) SARSCoV)	Swiss Webster (CFW) mice	Poly (D, L-lactidecoglycolide) 75:25 (PLGA)	Spike GP MPs + Alhydrogel® MPs + AddaVax™ MPs enhanced Expression of CD4+ and CD8+ T cells in secondary lymphoid organ like spleen and also spike GP-specific IgG, IgG1 and IgG2a antibodies in mice	[12]

Dissolving core–shell microneedles	Ovalbumin vaccination, Prevnar-13 vaccination	SAS Sprague Dawley rat	PLGA and polylactic acid (PLA)	Microneedles loaded with a clinically available vaccine (Prevnar-13) against the bacterium Streptococcus pneumoniae induced immune responses that were similar to immune responses observed after multiple subcutaneous bolus injections and led to immune protection against a lethal bacterial dose	[13]
Dissolving MN	H3N2 influenza vaccine	Female BALB/c mice	PLA	H3N2 microneedle vaccines elicited a Cross protective immune response against the H3N2 antigenic variants.	[14]
Microneedle Array Patch (MIMIX)	Influenza vaccine	Preclinical murine model	Silk fibroin	Immunization, higher HAI titers against drifted influenza strains	[15]
Dissolving Microneedle Patch (dMNP)	Polio vaccine and rotavirus vaccine	Female Wistar rats	Carboxymethylcellulose (CMC), polyvinyl alcohol and methylcellulose (MC).	IRV-IPV dMNP did not interfere with each other in triggering an immunologic response and were highly immunogenic in rats.	[16]
dMNP	Hepatitis B surface antigen (HBsAg) adjuvant free monovalent vaccine (AFV)	Female BALB/c mice and rhesus macaques	Maltodextrin and sucrose	Delivery of 10 µg (birth dose) AFV by dMNP induced protective levels of antibody responses in mice and rhesus macaques.	[17]

Microneedles are used to the delivery of molecules normally it is used to deliver the medication for instance: nucleic acids, proteins and vaccines because the medication can carry the medication throughout the body to absorb the medication. Currently, vaccine use is in the progress of their medication products, especially on the prevention of diseases and treatment purposes. There are novel and transdermal drug delivery such as microneedle remain over advantages than injection.

6. Conclusion

The auxiliary materials for transdermal drug delivery perhaps selected according to their different types, new technologies and forms of pharmaceutical preparations determined to certain situations. To explore chemistry physics and biology. Medication delivery through transdermal drug delivery

current trend is an effort on transdermal drug delivery and microneedle applications can be effective, safe and authorized in Malaysia and the overall health care system.

Transdermal drug delivery plays an important role in the treatment process nowadays in the study and treatment of chronic diseases and other diseases, for instance, diabetes patients and cancer patients who are suffering from these diseases are essential for their health care. Microneedles are to be study and explore for attempts to clear in each application of microneedles and also clinical aspects with the strongest evidence of the study.

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