A REVIEW ON: RECENT ADVANCES IN MICRONEEDLE DRUG DELIVERY SYSTEM

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***Abstract*- MN technology is a mode of active transdermal drug delivery and is intended to be used a as a replacement to the traditional syringe injections. The MN array is used to penetrate the stratum corneum and deliver the drug with a minimally invasive action. It offers several unique advantages: Large molecules can be administered, Painless administration of the active pharmaceutical ingredient, First-pass metabolism is avoided, Faster healing at injection site than with a hypo- dermic needle, No fear of needle, Ease of administration. There are different types of microneedle array patches such as solid MNs, through hollow MNs, Coated MNs and Dissolve MNs. The recent advance in Microneedle drug delivery system is that the Microneedle array patches which are used in various diseases like diabetes milletus, obesity, use n the treatment of cancer. Microneedle -Assisted NP Delivery in Vaccine Delivery**

***Keywords*: Transdermal drug delivery, Microneedle array patches, Diabetes milletus, Cancer etc.**

INTRODUCTION

MN technology is a mode of active Transdermal drug delivery and is intended to be used as a replacement to the traditional syringe injections. The MN array is used to penetrate the stratum corneum and deliver the drug with a minimally invasive action [1]. These arrays are micro-sized needles with a height ranging from 25 to 2000 µm [2]. MNs have been used for different applications such as drug and vaccine delivery, cosmetic, and disease diagnostics. MN have various structural arrangements, shapes, forms, and materials along with different manufacturing methods which are further illustrated in this review paper. Donnelly et al. argued that 30% of the most recent scientific literature in "Transdermal delivery technology" accounted for Microneedle studies [3]. MNs are micron-sized needles, which are large enough to deliver macromolecules, proteins, and vaccines into the different layers of (or across) the skin but are short enough to avoid any pain experienced as traditionally seen with the parenteral drug delivery. It offers several unique advantages: localization of small or large molecules in the skin by overcoming the SC barrier, placement of drug in the proximity to the blood vessels near dermis for faster absorption and onset of action during systemic delivery, targeting dendritic or Langerhans cells of immune system present in the dermis region which can be leveraged to develop vaccines; and eliminating pain [4, 5].

CLASSIFICATION OF MICRONEEDLE ARRAY PATCHES:

Solid MNs:

Generally, solid MNs are performed by creating the holes in the SC layer of skin and are applied before the application of dosage form and detached thereafter or the drug may be coated onto the needles. After removal of solid MNs, it leads to the formation of temporary microchannels where a drug can be placed in the form of cream, gel, solution, or Transdermal patches. These microchannels recover soon afterward so that there is no secondary infection [6,7]. The drug penetrates through the skin via microchannels and reaches to applicable site. In addition, solid MNs help to boost the Transdermal transmission of different biologicals or therapeutics, which cannot be conveyed by passive diffusion. Solid MNs can increase the Transdermal absorption of the small molecules by up to 4 folds. Additionally, these solid MNs are used to convey the bulky molecular weight compounds [7].conventionally ,small molecules of up to 500Da and molecules with log p of 1-3 are most suitable for topical administration .However ,once micropores have been generated using solid MNs, large molecules, including proteins and more hydrophilic drugs can slowly diffuse across MN generated micro-conduit.

Hollow MNs:

The method of drug delivery through hollow MNs involves the process of injection of drugs through a hollow bore, which is situated at the center of the needle. As the MNs are impaled into the skin, the hollow bore present inside bypasses the SC layer by creating microchannels into the different layers of the epidermis. The hollow bore enhances the transmission of activity via the needles either by diffusion method or by the pressure-driven flow. This method of approach is more reminiscent of an injection than a patch. It is used mostly for high molecular weight substances like proteins, vaccines, and oligonucleotides [8]. Drugs can be distributed as needed constantly, without the removal of drug patches as in solid MNs. These MNs are used for rapid bolus injection or slow infusion of the liquid formulation. Robust mechanical strength of micron-sized needles is necessary along with the adequate and constant flow rate. Dense dermal tissue might compress against the tip of the needle affecting the drug delivery rate and potentially targeting the wrong layer. Silicon is typically used for its high mechanical strength, but its high cost offsets its use in large-scale production. Hollow MN can directly place a drug in the ED-dermis region depending upon the length of the MN used making it possible to deliver macromolecules like proteins and vaccines. Insulin was delivered in the porcine skin using Admin Patch technology which uses hollow MNs. Hollow MNs can also be potentially useful in gene therapy as Luo et al. have demonstrated that localized delivery of oligonucleotides using hollow MN could be achieved in the 3D tissue model.

Coated MNs:
These are the solid array of MNs made up of different metals and silicon and then further coated with a drug or mixture of drugs. After applying coated MNs on the skin, the coated material gets absorbed into the skin followed by penetration. MN coating is considered a prominent technique for quick and instant bolus delivery of molecules [9]. In addition, appropriate coating and proper drying of drug or surface modification of smart MNs may enhance their long-term stability. Dip coating and casting techniques are most wisely applied for the production of coated MNs [10]. Depending on physicochemical adsorption, mechanism of chemical processing and surface alteration, numerous techniques, viz., dip coating, spray coating, and inkjet printing, brushing, electro hydrodynamic atomization, gas-jet drying, are used to produce coated MNs. Gill designed MNs along with central openings termed "pockets" that were prepared in aqueous or organic solvents. The flexibility of the MN coating technique was showed by coating curcumin (hydrophobic molecule) and bovine serum albumin (BSA)/insulin (model proteins) using suitable solvent-based coating solutions. Recently, transcutaneous vaccine delivery was investigated for the feasibility of fabrication and antigen delivery using coated MNs by Bhavnagar et al. As the layer of coating reduces, the mechanical strength as well as the sharpness of the MNs reduces, which confined the decrease in drug load on the surface of the MNs.

Dissolve MNs:
in the last few years, concerning the applicability of MNs, they are prominently used for the delivery of various kinds of compounds ranging from low molecular weight drugs to proteins, vaccines, and plasmid DNA. The literature survey evinced that the researcher increased the skin penetration of therapeutics like docetaxel by applying elastic liposomes to the skin and that was penetrated with silicon-based MNs, while some were coated with DNA using a water-soluble formulation. However, their expensive material costs or an unwanted two-step administration method limits the use of these types of MNs [11].To overcome these previously mentioned limitations, a biodegradable polymer or water-soluble carbohydrates have been utilized lately for the fabrication of MNs. This approach allowed the controlled release of drug from the reservoir after the formation of micro-conduits upon dissolving of MN tips. This approach can be pivotal in achieving the constant release of drug administration for prolonged pharmacological action, hallmarks for any medication intended to use in chronic disease management in the elderly population.

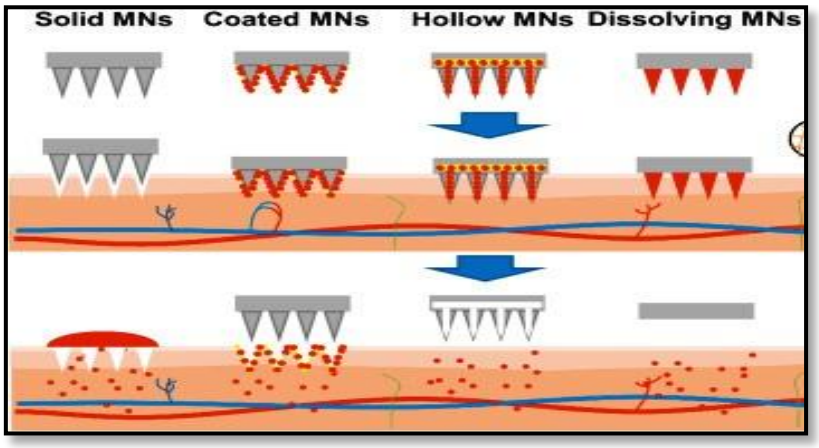


Fig.1 Classification of Microneedle array patches

Advantage of Microneedle:
(1) Large molecules can be administered,
(2) Painless administration of the active pharmaceutical ingredient,
(3) First-pass metabolism is avoided
(4) Faster healing at injection site than with a hypo- dermic needle,
(5) No fear of needle,
(6) Ease of administration

Disadvantages of Microneedle:
(1) Dosage accuracy may be less than with hypodermic needles,
(2) Careful use of the device may be needed to avoid particles 'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees,
(3) The thickness can lead to certain inconvenience in administration.

RECENT ADVANCES IN MICRONEEDLE DRUG DELIVERY SYSTEM:

MN-Assisted NP Delivery in Vaccine Delivery:
Most vaccines are currently administered using hypodermic needles, necessitating expert administration, cold chain storage, and the transportation of liquid formulations. In addition, most vaccines are formulated in liquid necessitating close temperature control during transport, storage, and distribution (i.e., cold chain) [12]. The issues of poor vaccine transport through the skin barrier, patient compliance, and cold chain can be addressed by MNs. MNs can painlessly bore the SC and canalize the epidermis to improve the vaccination as well as dependency on the cold chain and the need for reconstitution [13]. Additionally, MNs should be regarded as a unique strategy for the delivery of antigen to immune cells such as DCs within the skin, which is an essential problem in vaccine delivery. To date, MN reports have demonstrated similar or even higher immunogenicity and dose sparing [14]. Several investigations have reported the application of different MN strategies and their use in various vaccine formulations, including influenza, and

Human papillomavirus (HPV). For example, inactivated influenza virus vaccine was encapsulated in dMNs, and sucrose or trehalose was used to stabilize the antigen. The results indicated that the stabilization and vaccine drying through lyophilization can lead to greater vaccine stability and in vivo immunogenicity compared with the conventional vaccine preserved for 1 month at 45◦C [15]. Accordingly, dMNs can reduce the dependency on the cold chain, improve the thermo stability, eliminate the need for reconstitution, and simplifying vaccine distribution. For more detailed information regarding MNs-based vaccination systems, please refer to several excellent reviews. As mentioned earlier, MNs have contributed to the delivery of many NPs into the skin that can be extended to vaccine delivery. The main reason behind the use of NPs in combination with MNs to deliver the antigen is the improved stability and controlled release of antigen for inducing higher immunogenicity. For example, chicken OVA were encapsulated into PLGA-NPs, which were then incorporated in dMNs. Using this approach, MNs slowly released the antigen to lymph nodes occupied with DCs. This strategy led to the successful in vivo immune system activation against influenza and melanoma tumors. In another study, monophosphoryl lipid A, OVA, imiquimod, and Toll-like receptor (TLR) agonists were encapsulated in PLGA NPs, which were then intradermally delivered through hollow MNs. Unlike intramuscular injection, the MNs generated higher levels of IgG2a antibody and IFN-γ-producing lymphocyte [16]. Guangsheng et al. compared different types of nanocarriers to modulate the immune response by hollow MNs. To do so, OVA were loaded into MSNs, liposomes, PLGA, or gelatin NPs with or without polyinosinic: polycytidylic acid as an immunostimulant. Liposome and PLGA induced significantly higher IgG2a response. Moreover, liposomes led to CD4+ and CD8+ T cell activation [17].

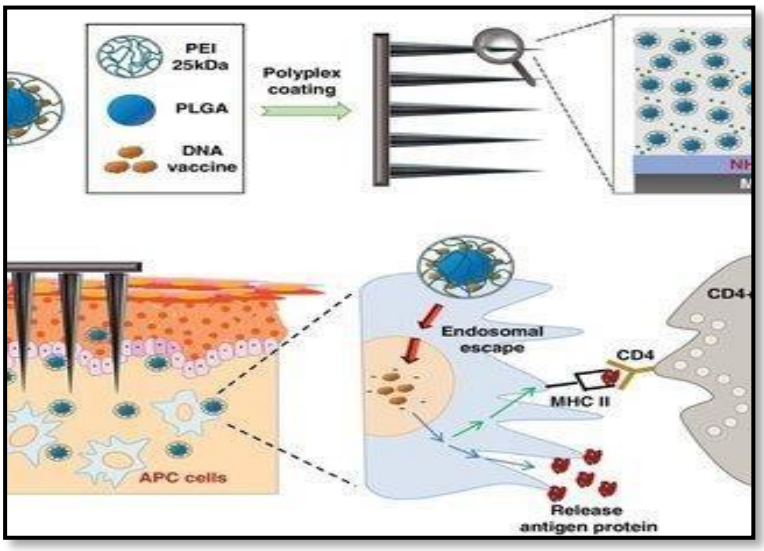


Fig.2: illustrationofthePLGA/PEI/pH1NIpolyplex-coatedMNforintradermalvaccination.

Microneedle array patches in diabetes milletus:

There have been various studies involving the use of MNs for diabetes management in humans and animal models. Biodegradable polymers in conjunction with dissolving MNs were used in diabetic rats, where a hypoglycemic effect was seen in a dose-dependent manner. Subcutaneous injection dropped blood-glucose levels below the hypoglycemic threshold, whereas the same dose of insulin delivered via MNs kept blood-glucose levels above the hypoglycemic threshold and maintained it at normal levels for longer periods, demonstrating the potential of MNs to deliver insulin in a controlled manner [18]. This was further substantiated in a different study by Resnik et al., where sustained plasma insulin concentration was achieved after the application of hollow MNs as compared to the same dose delivered by s.c. infusion [19]. Thus, in diabetes management, where often multiple doses are required; steady-state concentration of insulin can mimic multiple dosing regimens. In an innovative approach by Yanqi et al., biodegradable MN arrays were integrated with pancreatic β cells and glucose signal amplifiers. The presence of amplifiers triggered the release of insulin in a hyperglycemic state in type-1 diabetic mice and stabilized blood glucose levels over 10 hours. Potential of MN was also demonstrated in the pediatric population, where 16 children and adolescents received insulin via hollow MNs. MN insertion pain was significantly lower and the onset of action was significantly faster as compared to s.c. treated arm indicating potentially greater patient compliance in children for the treatment of diabetes, as they are often afraid of needles. From the diagnostic point of view, MNs have been studied as the means of continuous glucose monitoring systems (CGMS). MNs are functionalized either to act as a sensing probe or a biological fluid collector. Both approaches have their unique challenges as it is quite difficult to develop functionalized MNs in a miniature form.

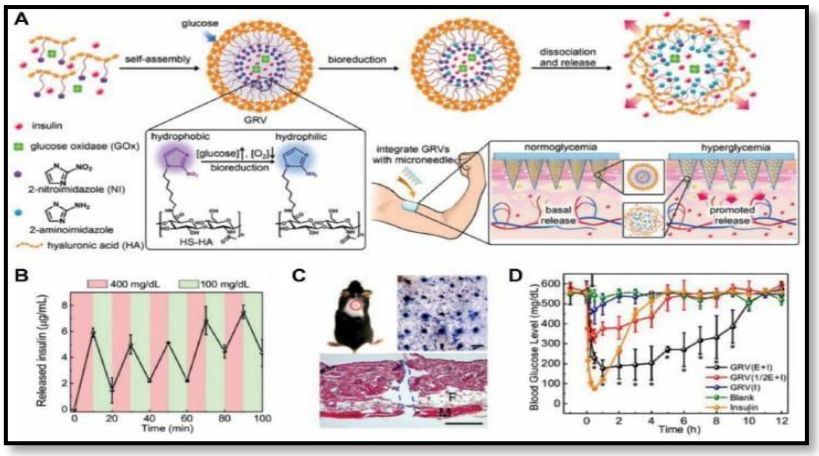
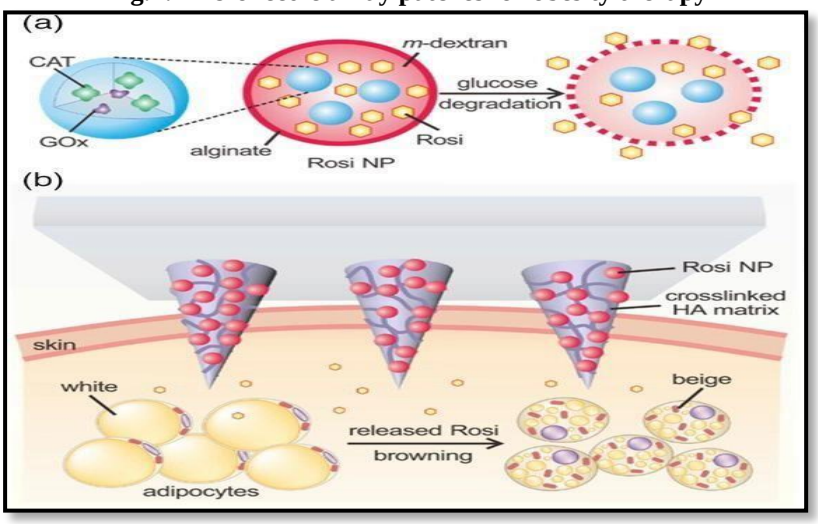


Fig.3: Microneedle array patches used for diabetes milletus treatment.

Obesity:

Obesity most often results from excessive accumulation of fat, caused by the imbalance of fat absorption and energy expenditure. Meanwhile, environmental and genetic factors also play important roles in the development of obesity. Dietary and lifestyle adjustments can facilitate weight management, but it is difficult to maintain for a long period. Nowadays, with the development of nanotechnology in obesity treatment, the integration of NPs encapsulating anti-obesity drugs with MN patches has also been more extensively explored for obesity treatment. Several nanomedicine-based obesity treatments have manifested enhanced efficiency and reduced side effects. Zhang et al. prepared a degradable cross-linked HA-based MN patch consisted of browning agent-loaded pH-responsive dextran NPs for obesity therapy. GOx and CAT were also encapsulated into the dextran NPs. GOx was used to lower the local pH level under physiological glucose concentration via the conversion of glucose to gluconic acid, whereas CAT was used to consume undesired H_2O_2. Cross-linked HA promised sufficient stiffness of the MNs. Under the physiological glucose condition, the pH-sensitive nanoparticle gradually degraded in an enzyme-induced acidic environment to subsequently release the embedded browning agents to adipocytes and promote their transformation from energy storing (white) to energy expenditure (beige). . In order to achieve high therapeutic efficacy, a desirable anti-obesity treatment requires adipocytes-specific delivery of drugs with a low dose. The Microneedle-based device provides a localized and bloodless delivery strategy, which is able to maximize the therapeutic effect with a minimal drug dosage. Anti-obesity drug delivery utilizing Microneedle patch has been demonstrated potential in weight management [20]. This painless administration method can not only enhance the therapeutic efficiency due to the concentrated drug level within adipose tissue, but also overcome the adverse effects caused by systemic administration.

Fig.4: Microneedle array patches for obesity therapy



Cancer:

Traditional treatment regimens including surgery, chemo therapy and radiotherapy can lead to acute toxicity and side effects as well as tumor recurrence. A minimally invasive cancer treatment associated with microneedle patches always appeals broad interest as a result of advantageous controllability, easy applicability and predominant synergistic effect [21]. Considering the depth of MN insertion, the drugs can easily target the lymph capillaries. MNs are an elegant device for tumor metastasis or for improving human immune response. Kong and co-workers prepared HA-based doxorubicin-loaded transfersome (DOX-T)/MN complex for the treatment of metastatic tumors. The substrate and arrays of MNs were made from dissolvable HA, and DOX-T was filled in the tips of the needles (Fig.5). Once inserted into the skin, the preloaded transfersomes could be released into the dermis with the dissolving of HA, thereby enhancing the distribution of the entrapped DOX in lymph nodes. The integration of MNs with transfersomes breaks the limit of transdermal transit while enhancing lymphatic delivery. Their results confirmed the efficient insertion of MNs into the skin and the efficient lymphatic delivery of preloaded DOX. Compared with epidermal diffusion, DOX-T/MN dramatically

promoted lymphatic delivery of DOX in Sprague-Dawley rats.

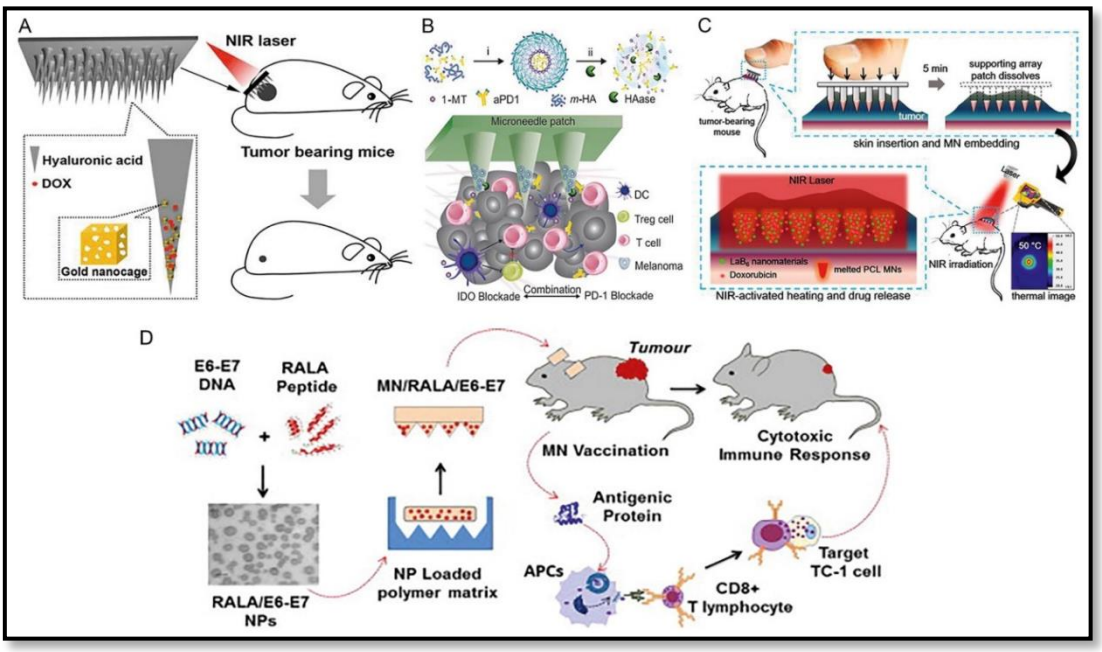


Fig. 5: (A) Dissolvable microneedle arrays made from HA containing chemotherapeutic drug DOX were integrated with gold nanocages followed by exposure to NIR light to combine chemotherapy with photothermal therapy for synergistically treating superficial tumors. (B) A microneedle platform based on HA was encapsulated anti-PD1 antibody to combine with the PD1 and 1-MT to inhibit IDO for melanoma immunotherapy. (C) A light-activatable microneedle patch was composed of dissolvable PVA/PVP as supporting material containing polycaprolactone formulation, which consisted of photothermal nanoparticles and an antitumor drug for treating skin tumors synergistically. While exposed to NIR light, the microneedle patch was melted at 50 C to release DOX for loco regional cancer therapy. (D) The polymeric polyvinyl pyrrolidone microneedle patch brought together two main components including the peptide RALA and DNA vaccine for the treatment of cervical cancer.

CONCLUSION

As an emerging device, Microneedle possesses characteristic advantages (painless and rapid delivery) as compared to other systemic administration. This paper summarizes MNs technology in the transdermal drug delivery era. Extensive studies and research have been conducted in the fabrication of MNs due to its advantages. Various types of microneedle array patches such as solid MNs, through hollow MNs, Coated MNs and Dissolve MNs and its advantages, moreover this review articles state about the recent advances in the Microneedle array patches which are usedin the treatment of various diseases like diabetes milletus, obesity, use n the treatment of cancer. Microneedle -Assisted NP Delivery in Vaccine Delivery.

ABBREVIATION

MN-Microneedle
SC - Subcutaneous
Da– Dalton
ED- Epidermis
DNA – Deoxyribonucleic acid
HA-based – Hollow Array
GOX - Glucose oxidase
CAT –Catalase
H_2O_2- Hydrogen peroxide
NPs - Nanoparticles

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