Global Research journal of Natural Science and Technology (Grjnst)
Volume: 03 - Issue 1 (2025)
p.ISSN: 2790-7643e.ISSN: 2790-7651

Microneedle-Based Drug Delivery Systems: A Comprehensive Review of Biomedical Applications

Sasuee Khatoon

Institute of Biomedical Engineering and Technology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

Sasuee.khatoon@lumhs.edu.pk

Sehreen Moorat

Institute of Biomedical Engineering and Technology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

sehreen.moorat@lumhs.edu.pk

Natasha Mukhtiar

Institute of Biomedical Engineering and Technology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

Natasha.mukhtiar@lumhs.edu.pk

Muhammad Ali Bohyo

Institute of Biomedical Engineering and Technology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

ali@lumhs.edu.pk

Manahil Siddique

Institute of Biomedical Engineering and Technology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

manahil.siddique19@gmail.com

DOI:https://doi.org/10.53762/grjnst.03.01.41

CC BY

Abstract

In recent years, microneedle technology has emerged as a significant advancement in biomedical engineering, offering a minimally invasive and patient-centered approach to therapeutic delivery. Conventional drug administration methods, such as hypodermic injections and systemic dosing, are often limited by pain, poor patient adherence, low bioavailability, and unwanted systemic side effects. To overcome these limitations, microneedle-based delivery systems have been extensively investigated for applications in cancer therapy, diabetes management, wound healing, and ophthalmology. This review outlines recent progress in microneedle fabrication, material selection, and functional design, with particular attention to their use in localized anticancer treatment, transdermal insulin delivery, hemostatic wound care, and ocular drug administration. Various microneedle designs—including solid, hollow, coated, dissolving, and hydrogel configurations—are examined in relation to their capacity for controlled drug release, effective tissue penetration, and reduced systemic exposure. While preclinical studies demonstrate encouraging therapeutic outcomes, several obstacles continue to impede clinical translation, including concerns related to long-term safety, incomplete pharmacokinetic understanding, manufacturing scalability, and regulatory approval. Despite these challenges, microneedle technology remains a highly adaptable and promising platform for future drug delivery, provided that issues of biocompatibility, standardization, and clinical validation are systematically resolved.

Keywords: Microneedles, Transdermal drug delivery, Cancer therapy, Insulin delivery, Wound healing, Applications of microneedles in bioscience

1. Introduction

In the field of biomedical engineering, the delivery of therapeutic agents has great impact for diagnosis, disease prevention and therapy. Even though the conventional used techniques like hypodermic injections, oral medicines and other widely used techniques have several drawbacks. Their efficacy is challenged by uneven drug absorption, poor patient compliance and unfavorable consequences which may lead to different health issues. The repeated hypodermic injection at the site of drug may lead to localized tissue damage and discomfort. In this regard, microneedling based drug delivery technique combines the advantages of injectable treatments and transdermal administrations. Microneedles are tiny needles that are intended to penetrate stratum corneum i.e. superficial skin barrier without pain or causing vascular damage. Microneedles allow the delivery of various therapeutic drugs including nanoparticles, vaccines, and proteins. Due to the less invasive nature of microneedling technique it is ideal for patient and clinical treatments which makes it ideal for both. Significant progress has been made in the microneedling industry over the past 20 years in polymer engineering, microfabrication and materials science. A variety of microneedle designs have been offered depending on the desired use which includes, hollow, dissolving, coated and hydrogel-based forms. These microneedles are designed to distribute drug in a sustained and controlled way that may respond to external and biological stimuli. In cancer therapy, microneedling help to reduce systematic toxicity by facilitating localized delivery of chemotherapeutic drugs, gene based treatments and immunotherapies for superficial cancers. Whereas, in diabetes microneedles assist insulin administration and patient monitoring more friendly than the regular hypodermic injections. Also, microneedles have various applications in the field of wound healing and ophthalmology to support tissue regeneration and overcome ocular barriers to increase the medication distribution respectively.

This paper presents a comprehensive review of microneedling technology applications in biomedical engineering with particular focus in cancer therapy, wound healing, ophthalmology and diabetes management. Moreover, this review outlines the current developments and limitations in the growing role of microneedles.

Cancer Therapy

In recent years it is estimated that cancer remains one of the life threatening disease and its ratio multiplies day by day in accordance to present data. At the same medical sciences have shown great advancement for introducing new techniques to treat cancer rightly because sometime it is shown that anticancer therapies based on nanoparticle have been effected severely due to low capacity accumulate within tumor's cells even below 1% of administered dose at target cells [1]. Therefore; to avoid the complexities in the Nano medicine and drug delivery system for redesigning therapeutic outcomes, researchers started to remodel and re-explore microneedle technology that is more effective in local and controlled delivery of the therapeutic nanoparticles at the site of tumor cells [2,3]. Based on research and preclinical evaluation have been carried out to validate the different applications of microneedles for drug delivery systems in this digital era. The scientific committee had reviewed that Cancer vaccination has been revealing promising anticancer results. At the same time, the advantage of utilizing microneedles is to overcome the skin's stratum corneum layer and comparatively reduce discomfort and avoid pain of hypodermic needle insertion in the skin, as microneedles enhance thermos-ability at that region. As skin is considered as largest organ of the human body and it work as barrier wall to resist exogenous material. Below Figure.1.1 shows the microneedle representation working on anticancer therapy purpose while stabilizing immune cells activating an antitumor response by host.

André F. Moreira, Carolina F. Rodrigues et.al; reviewed the importance of microneedles at macroscale drug delivery system locally mediate for tumor cells and reduce the discomfort and avoid complications associating to drug delivery system of therapeutics. Besides, advantages of microneedles applications in therapy there are disadvantages discussed here due to designing of microneedle based on different materials. On the basis of penetration author also reviewed different microneedles penetration in the skin to inhabit the growth of tumor cells as summarized in following Table.1.1 [4].

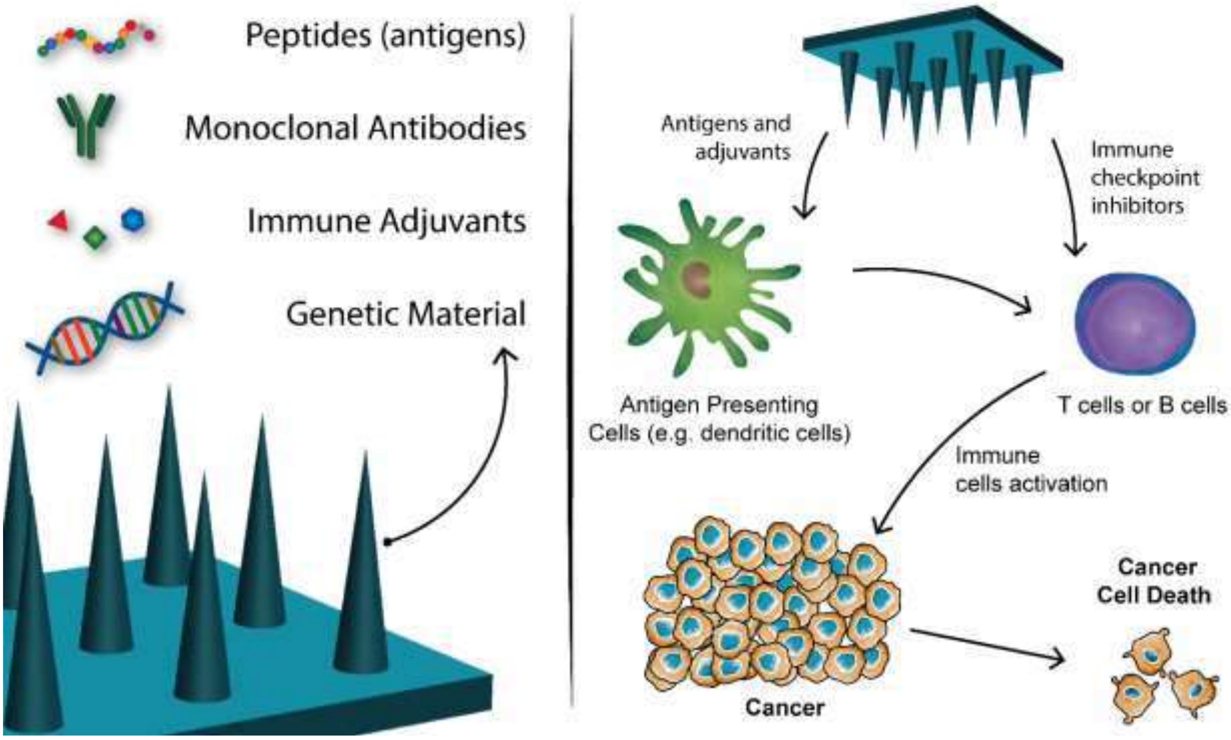

FIGURE 1.1 THE MICRONEEDLE'S APPLICATION TREATING ANTICANCER THERAPY WHILE LOADING NANOPARTICLES, I.E. IMMUNE ADJUVANTS, ANTIGENS, ANTIBODIES (MONOCLONAL ANTIBODIES).

TABLE 1.1 SUMMARIZED ANALYSIS OF MICRONEEDLES IN IN-VIVO CANCER THERAPY

Microneedle Material	Design Method	Therapeutic agent	Microneedle Size	Model preferred	Type of Study	Analysis
Dextran, polyvinyl pyrrolidone, and hyaluronic acid[1]	Micromoulding 12x12 arrays	STAT3 siRNA/ polyethyleni mine complexes	Height: 650 µm; Base width: 300 µm	B16F10 tumorbearing C57Bl/6 mice	*In vivo*	Decreased the tumor growth, tumor weight 5 times inferior to control
Polyvinyl alcohol[2]	Micromoulding 19x19 arrays	RALA/E6 and E7 pDNA	Height: 600 µm; Base width: 300 µm;	TC-1 tumorbearing C57 BL/6 mice	*In vivo*	Microneedles administration increased the antigen specific IgG

						and decreased the tumor growth
Pluronic F127/Poly (ethylene glycol)[3]	Micromoulding 7x7 arrays	OVA and R848	Height: 350 µm	HCT116 tumorbearing C57BL/6 mice	*In vivo*	Increased mice survival and decreases the tumor growth
Polyvinyl pyrrolidone[4]	Micromoulding 19x19 arrays	RALA-E6/E7 DNA nanoparticles	Height: 600 µm; Base width:300 µm	TC-1 tumorbearing C57BL/6 mice	*In vivo*	Increased mice survival and decreases the tumor growth
Hyaluronic acid[5]	Micromoulding 9x9 arrays	aPD1 and glucose oxidase	Height: 600 µm; Base width: 300 µm	B16F10 tumorbearing C57BL/6 mice	*In vivo*	Increased mice survival and impaired the tumor growth
Hyaluronic acid[6]	Micromoulding 15x15 arrays	1-methyl-DLtryptophan and aPD1	Height: 800 µm; Base width: 300 µm	B16.OVA melanomabearing mice	*In vivo*	Increased the infiltration of effector T cells to the tumor tissue. Impaired the tumor growth,
Methylvinylether and maleic anhydride[7]	Micromoulding 19x19 arrays	Ovalbumin loaded poly (D,Llactide-coglycolide)	Height: 600 µm;	B16.OVA melanomabearing	*In vivo*	Triggered the activation of effector T cells and prevented

		nanoparticles		mice		the establishment of ovalbumin expressing B16 melanoma tumors.
AdminPen[8]	Array with 43 microneedles	Microparticle loaded with whole cell lysate of ID8 ovarian cancer cells	Height: 1100 nm	ID8 tumor bearing C57BL/6 mice	In vivo	Decreased tumor growth and increased amount of effector T cells

Dongdong Li, Doudou Hu et al; reviewed and tested preclinical and technical perspectives of microneedle for treatment of tumor cells through chemical therapy, immunotherapy, gene therapy, photo thermal therapy and through antibody. In this review transdermal drug delivery is also seen as highly encouraging perspective especially through superficial drug administration in skin as shown in Figure.2

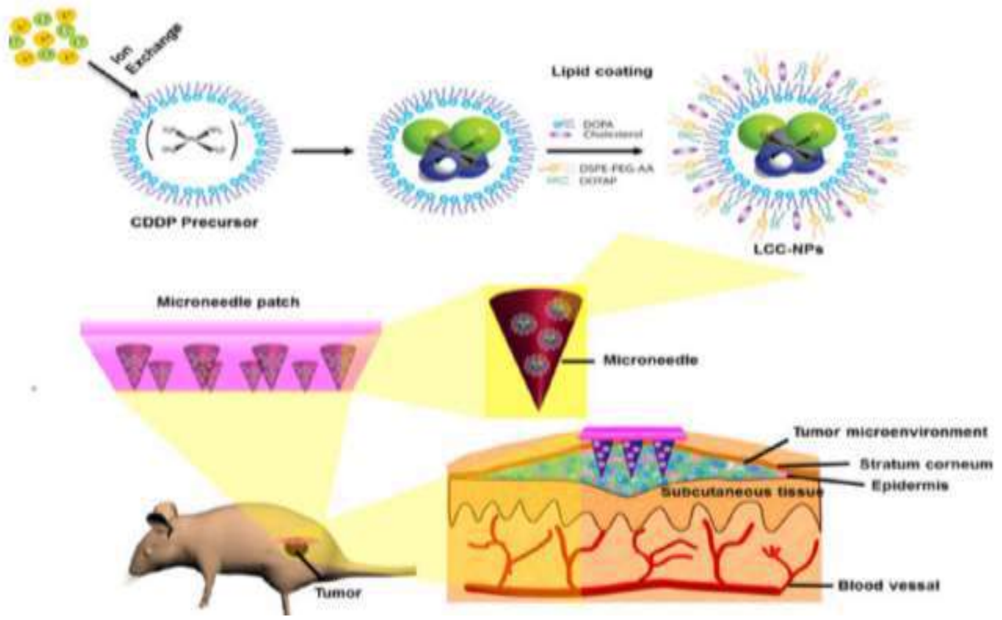

FIGURE 2.2 ILLUSTRATION OF ANTICANCER THERAPY THROUGH TRANSDERMAL DRUG DELIVERY USING LIPID-COATED NANOPARTICLES

Author also had made some suggestions about cancer therapy that can reduce the hurdles and side effects of Microneedle while treating tumor cells. According to reviewer metastatic cancer should be focused instead of superficial cancer because immunotherapy will be effective in this condition and restrict and eradicate the spread of cancerous cells towards healthier cells in the body. At the same time there is risk of side effects of treating tumor while injecting nanoparticles using microneedles that may block the antibody or cytokines, to prevent the allergic reaction or any type of side effects there should be alternative strategy while using microneedles loaded with nanoparticles. Author also studied that there is lack of bioavailability and pharmacokinetic information for clinical translation and at the safe time safety usage of microneedle is also seems to be ignored for long term side effects evaluation. At the last it is also reviewed that biocompatibility of Microneedles should be considered for the cancer therapy [5]. Meng Wang · Xiaodan Li et al; Studied and reviewed the superficial tumor that is treated by different types of microneedles and Microneedle-mediated treatment and diagnosis of superficial tumors (Breast cancer, squamous cell carcinoma, head and neck carcinoma, human oral epidermoid carcinoma, and melanoma). In nineteenth century it was observed that lymphadenectomy and surgical resection was the only option to treat superficial cancer like melanoma then in twenty centuries, chemotherapy become breakthrough to kill the cancerous cells but the toxicity of chemotherapy drug reduces the survival rate of superficial carcinoma patients. At present, carcinoma cells are treated through radiotherapy and immunosuppression. In non-melanoma superficial cancer assigned targeted delivery of drugs i.e. coded gene molecules, enzyme inhibitors, chemotherapy drugs, monoclonal antibodies to see efficacy and better therapy prospects [6]. Author represented the role of all four types of needle through flow chart as shown in Figure.3. He described that upside- down pushpin having sharp tips (Solid MNs) were first used in 1990 due to rise of microfabrication technology. But it was seen that due to insertion metallic solid needles, causes irritation, swelling, discoloration of skin. Then hallow microneedles were introduced. The main advantage of hallow needle was to deliver small quantity of drug at targeted cells as compared to solid needle effectively within 10hrs and have been able to deliver 2ml of fluid and deposit about 75% administered drug at the targeted cells within body even though design of hallow needles is complex. The beginning of twenty-first century become the era of technology, in this era dissolving MNs ad Coated MNs become most demanding due to their design and were biocompatible in nature without affecting skin after repeating application of needles. As dissolving needles become back through at the present time due to ecofriendly and biocompatibility [6]. It is therefore; summarized that microneedles play vital role in superficial cancer while delivering drug to the tumoral cells. At the same time, it is observed that drug delivery through these needles take time to deliver and deposit about 70%-75% in the skin. There should be some consideration at the time of design that needles should deliver drug in less time and more effectively without damaging healthier tissues in the body. In short it is also seen that whole research is about superficial cancer but not about metastatic cancer cell. So if we take step while considering metastatic cancer then we can stop the spreading tumor cell towards other cells.

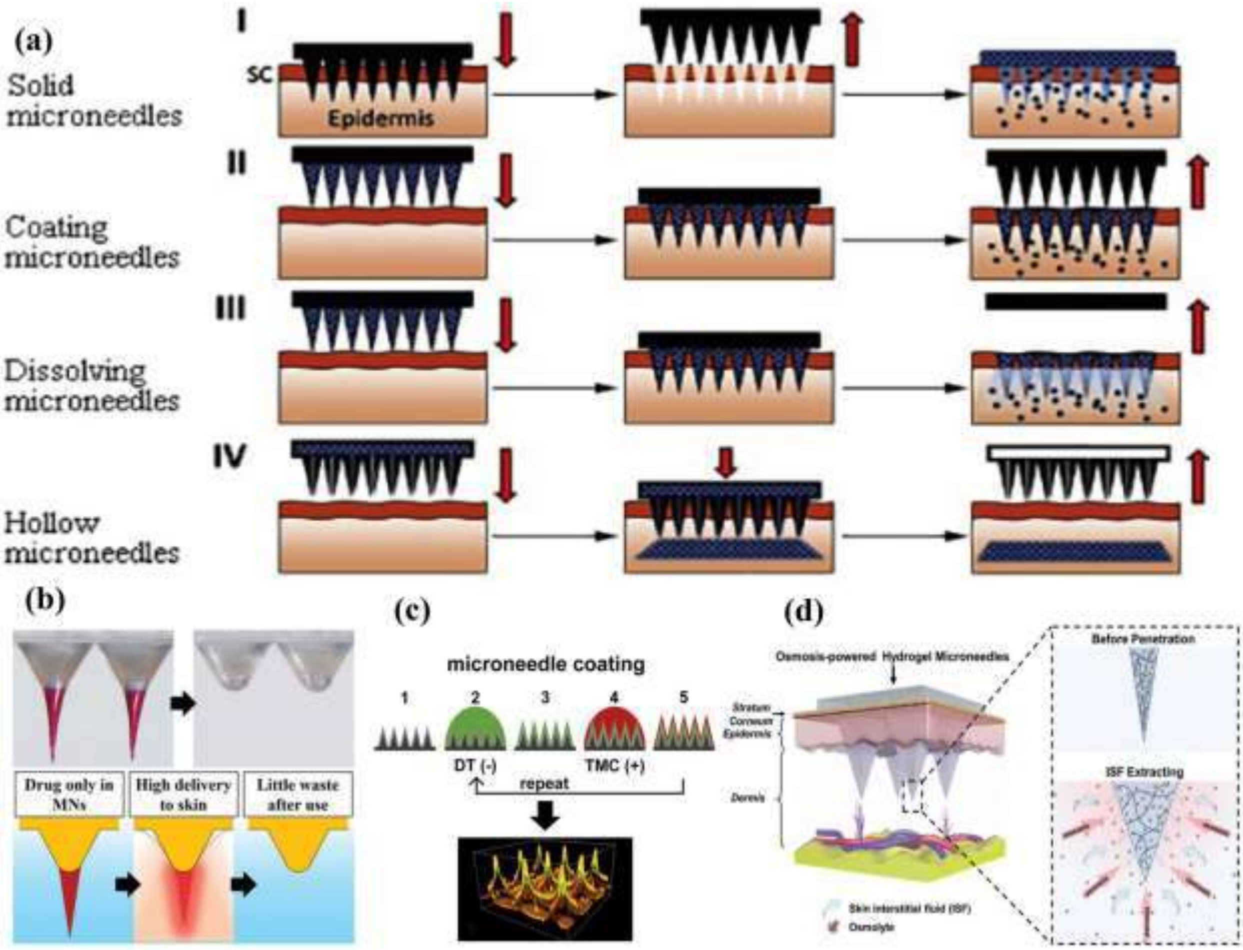

FIGURE 3. (A) ILLUSTRATION OF ALL FOUR TYPES OF MNS (SOLID MNS, HALLOW MNS, DISSOLVING MNS AND COATED MNS) THROUGH FLOW CHART, (B) REPRESENT DISSOLVING MNS, (C) REPRESENT COATED MNS AND (D) HYDROGEL MNS

2. Applications of Microneedles in Diabetic Therapy

In the era of Technology, the advancements in Technology harnessed its strong roots not only in medical sciences but in engineering also. When we talking about emerging scope of technology in medical sciences, it is important to know the scope of microneedles in clinical perspectives for different therapies i.e.; cancer therapy, wound healing, drug delivery, diabetic therapy and in cardiovascular disease [7-8-9]. As we know that in the transdermal delivery system the skin is considered as Absorptive organ. Based on research, compared to conventional hypodermic needles microneedles are considered to be painless, biocompatible because the nature of material used in design of MNs allows both micro molecules and macromolecules of drug to enter into and across the skin. This review is about Diabetes Mellitus and drug delivery of insulin through microneedles with highly compatible, dosage insertion and therapeutic stability. One of the most complicated and debilitating illness Type-1 Diabetes Mellitus due to inability of β-cells within the pancreas, to release a suitable quantity of insulin to regulate blood glucose level [10-11]. This condition has long term negative impacts like diabetic ketoacidosis, peripheral vascular disease per-pr cardiovascular disease, cerebrovascular disease, neuropathy, retinopathy and nephropathy at macro vascular and microvascular level diseases. In this article author reviewed clinical translation of needles on the basis of benefits including painless nature of needle in comparison to conventional hypodermic microneedles, simplicity and can easily be administered by diabetic patients as clinical benefits. Moreover, it is also seen that frequent usage of drug in case of insulin is of clinical importance, in that case hallow needles considered to be most favorable in repetitive application of insulin. On the other hand, there are unmet clinical hurdles including material compatibility in design, disposal and sterilization should be considered while using [12-13-14]. Yang Zhang worked on as-prepared microneedles based on maltose (Ca2+/Alg-Mal) composite have been considered for the application of insulin delivery via in vivo on diabetic Sprague-Dawley (SD) rat models because of strong mechanical and high compatibility. An effective and potential application of as-prepared Ca2+/Alg-Mal needles while using encapsulated insulin have excellent results as compare to subcutaneous injection route the highest failure force about 0.41 N/needle [8].

3. Wound Healing

Hemostasis is one of the medical concerns which means that body’s reaction to any injury to stop bleeding. To initialize effective and rapid hemostatic material based patches including fibrin -glue, adhesives (polyethylene glycol) and polydopamine-derived gels have been designed. Hemostatic abilities based on chemical relation between tissues and patches that stop the bleeding and promote the blood clotting while not considered for hemophilic patients having clotting disorder [15-16-17]. Xiaoxuan Zhang suggested DCS coated pagoda-like microneedle patch for effective hemostasis and tissue healing process in case of sting of insects i.e., ladybugs, wasp and gadflies. Author shown tremendous results by applying dodecyl-modified chitosan-coated pagoda-like multilayer needle patches on acute tissue injuries in liver, kidney and spleen of rabbit. These types of DCS-coated Patches fabricated for acute injuries like visceral bleeding and shown biocompatible and could become promising candidates while dealing in wound, healing acute injuries and so on, well elaborated as in given Figure.4 [4].

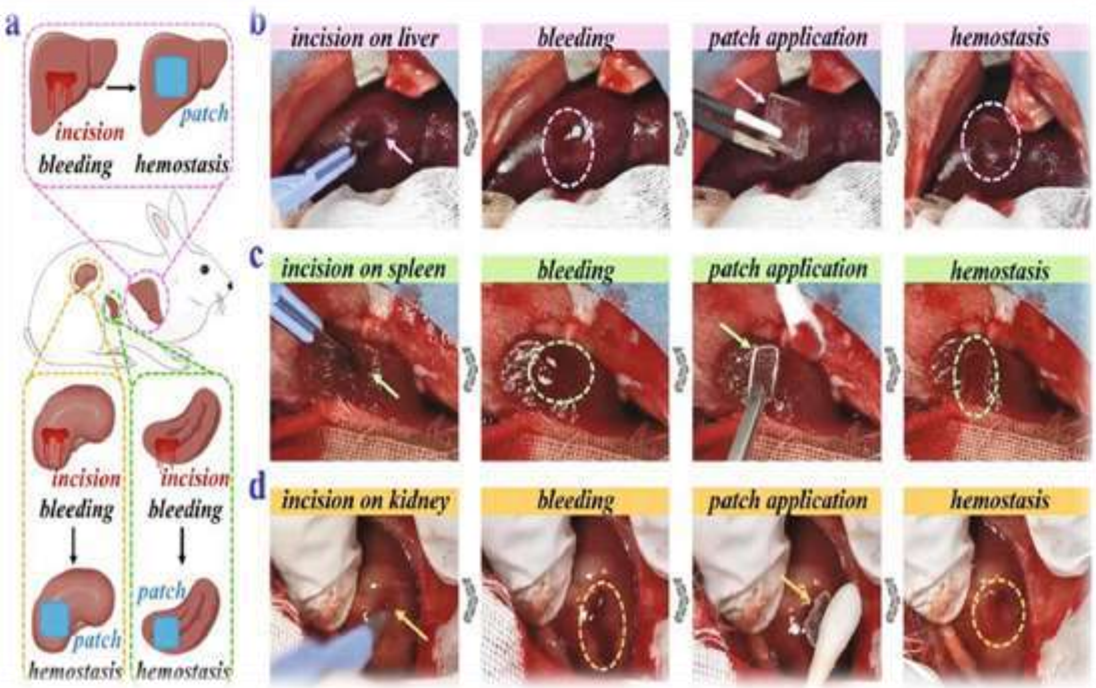

FIGURE 4. (A) DEMONSTRATION OF IN-VIVO HEMOSTATIC STABILITY OF DCS-COATED MICROSTRUCTURE NEEDLE PATCHES WHILE STUDYING RABBIT LIVER, KIDNEY AND SPLEEN, (B) SHOWS THE HEMOSTATIC EFFECTIVENESS IN TREATING RABBIT LIVER, (C) ILLUSTRATE THE TREATMENT OF SPLEEN THROUGH

Jinying Lv, Hongyu Ma, Gengsheng Ye et al., designed bilayer microneedle i.e. CS-AS-BSP (chitosan (CS)/Bletilla striata polysaccharide (BSP) composite containing asiaticoside most efficient in wound healing without anti-inflammatory effect. In this research centrifugation Technique has been applied for wound healing with a polydimethylsiloxane mould. This type of transdermal drug delivery through bilayer dissolvable needle have reduced the effect of human scar fibroblast containing fibrosis-related genes (TGF-b1 and COL I). The summarized results have shown that CS-AS-BSP bilayer needle from clinical point of view have great influence in biomedical field with new strategy to heal wounds within weeks' scar-less and antibacterial effect [18]. Despite more than ten years' research have been done on variety of dissolving/hydrogel micro structured microneedles in wound healing and regeneration of tissues that took longer time to heal and might cause inflammatory effect at the side of damaged tissue. It is reviewed that their multilayered microneedles play curious role in acute injuries of spinal cord, liver, kidney, spleen, cornea, skin and so on but still there is need to microneedle for ISTR. ISTR is convenient method to carry out patient's own cells as drug, gene, polypeptide and growth factors to regenerate tissues through stem cells. As Neuro-Gene and Neurotube have been applied in case of nerve repair. In the same way for orthopedic applications bone graft are utilized. Herein basic design assumptions of functional microneedles have been considered for ISTR as illustrated in Figure.5. [19].

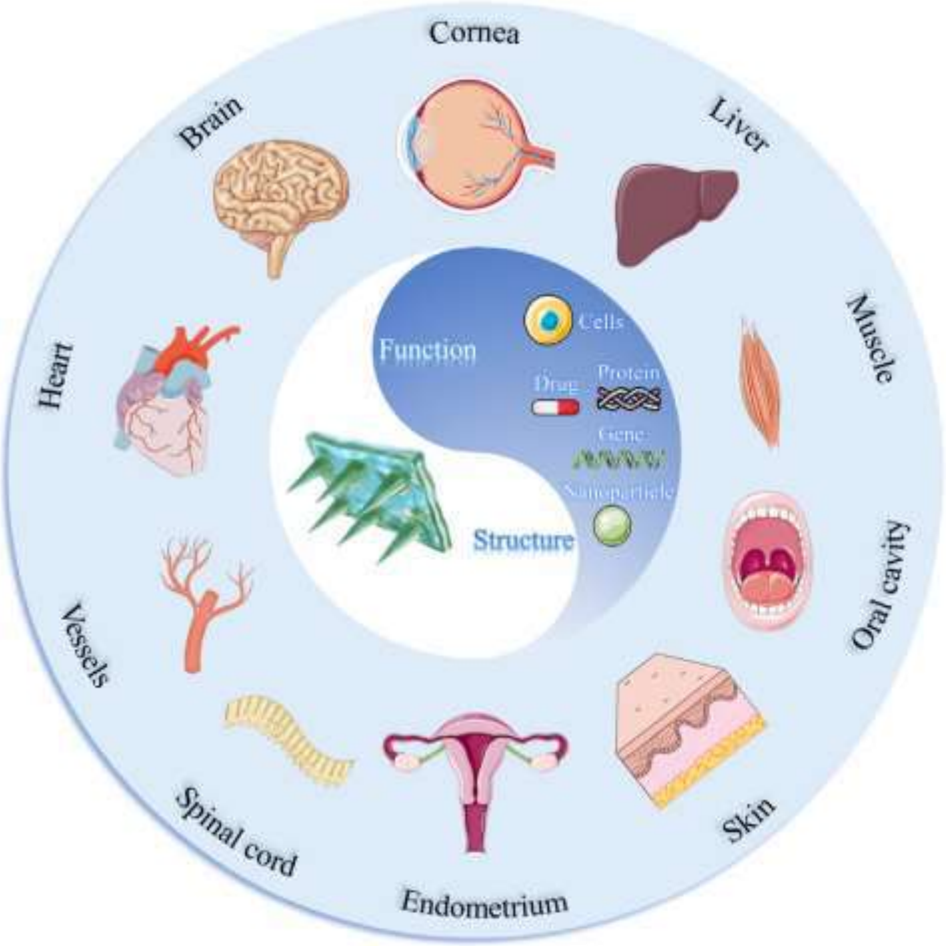

FIGURE 5. DIAGRAMMATIC REPRESENTATION OF FUNCTIONAL MICROSTRUCTURE NEEDLES FOR IN SITU TISSUE REGENERATION

Based on types of microneedles are categorized while analyzing anti-inflammatory effect, anti-bacterial effect, wound healing, drug delivery effectively, scar-free-effect and proliferation of skin and so on. The categorical design with respect to their effectiveness, biocompatibility, bioavailability and engineering biomaterial of microneedles fulfill the clinical promises.

4. Ophthalmology

Beside different applications of micro structured needles in the biomedical field, microneedles have promising clinical importance in the field of ophthalmology. As eye is the sensitive organ of human body. Human eye from structure point of view is segmented into two parts i.e., anterior part and posterior part. An anterior part of eye containing cornea, iris, aqueous humor, ciliary body, conjunctiva excluding the sclera, retina, choroid, optic nerve forms that make the posterior part of the human eye. cataract, glaucoma, conjunctivitis, anterior uveitis while posterior segment diseases include age related macular dysfunction (AMD), diabetic retinopathy, retinitis pigmentosa (RP) are the anterior and posterior diseases respectively [20].

These diseases cause person with vision loss either partially or completely depends on severity and early diagnosis is considered the first step to cure disease and prevent vision loss. So, different treatment methods have been implied like conventional drug delivery to fix vision loss timely. It was seen that drug delivery through intraocular injections like IVT, Periocular, intra corneal, sub-conjunctivial are advised for treatment but have less availability and are invasive in nature. To reduce drawbacks of conventional drug delivery and make more impactful method through compact, micro-structured needles. These microneedles/Nano-devices assumed as biocompatible, disposal in nature, scar less effect, painless, and minimal noninvasive in nature and are considered when there is need of repetitive application while treating disease. Due to anterior/ posterior segment barriers, it seems to be challenging task to deliver drug in the eye. Microneedles like solid, hallow needles have been used to deliver medication to the eye part. At the same time, it is also seen that there are some drawbacks while using these micro-structured needle whereas, dissolving polymeric needles are more biocompatible, easy to handle, painless in repetitive usage, biodegradable and so on. Dissolving polymeric MNs are fabricated well with biodegradable polymers. The technique of using dissolving microneedle in two steps, in first step microneedle patch is applied to ocular tissues and in second step the medicine that is delivered through this Nano-device patch will be released within tissues that is demonstrated in Figure.6. [21-22]. At present, posterior segment disease considered to be more fatal will also affect anterior segment of eye. For example, Diabetic retinopathy causes blindness if not diagnosed on time because main cause of DR is Diabetes. At the same time decreased light transmittance occurs due to crystal formation and fluid turbidity. So the diagnosis is possible through visual inspection and optical ophthalmoscope make the convenient to see fundus image after dilation of pupil. [23]. Herein, hollow MNs were mostly used to overcome compliance of patients regarding discomfort, enable self-administration. Different attempts were made to deliver sulforhodamine B solution and was observed after twenty seconds of insertion of dye-loaded needle that the dissolution of medication delivered to the tissue possible. In the same way other microneedles were become successful to deliver the medication to eye like bevacizumab incorporated to treat corneal neovascularization using microneedles. [24].

From above study it is analyzed that microneedles become the most advanced technology to cure diseases at clinical bases. Trials made the possibility to incorporate the drug delivery through these micro-structured devices. They are biocompatible, bioavailable, painless, easy to handle, reduces discomfort, scarless effect and so on. On the other hand; making some trials on other species like rabbit. A pilot study in rabbit was undertaken to analyze toxicity profile of microneedle (Methotrexate -2mm length) using solvent cast technique through poly (D, L-lactide). These histopathological observations give us conformation that new emerging technology based micro devices are most impactful and have no adverse effects on human.

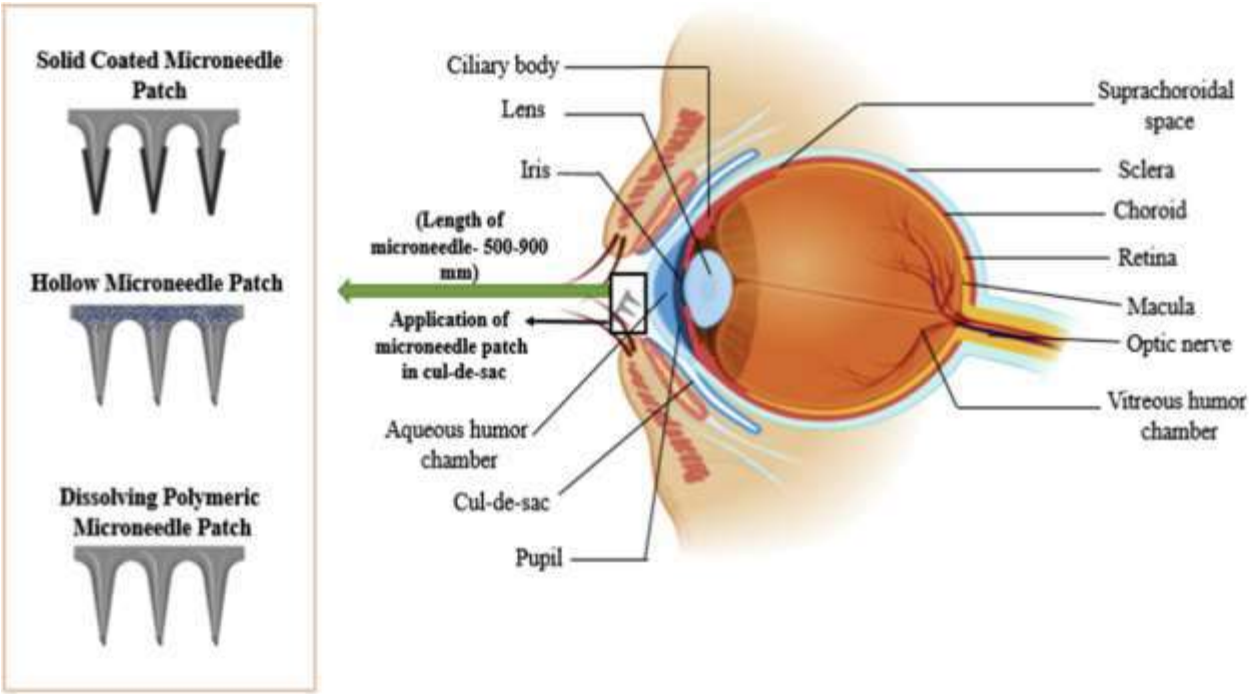

FIGURE 6. SCHEMATIC ILLUSTRATION OF HUMAN FUNDUS IMAGE AND THREE DIFFERENT PATCHES INCORPORATED IN CUL-DE-SAC FOR MEDICATION DELIVERY IN EYE.

5. Conclusion

Microneedling technology provides significant benefits over many conventional drug administration techniques. Its minimal invasive nature helps to improve treatment adherence, reduce patient discomfort and also limits unwanted systematic effects. As discussed in this review, microneedling based system have shown promising results in several clinical applications. In cancer treatment, it helps in localize delivery of drug to enhance therapeutic effect of drug without harming surrounding tissues. In diabetes, long term insulin control and delivery is possible without repeating painful injections. The improved tissue repair and rapid bleeding control is also possible with the help of microneedle patch when it is applied on the wound which provides the best results in the wound healing. However, in the field of ophthalmology, these microneedle patch overcome ocular barrier and provides improved drug delivery to the challenging sites. Despite many of these advantages, several limitations provide obstacle in the adaptation of microneedling technology in medical field. Few key challenges are; clear understanding of drug distribution, long term safety and biocompatibility data. However, the manufacturing process, regulatory pathways and industry pathways also plays a vital role.

REFERENCE

[1] C. F. Rodrigues, T. A. Jacinto, A. F. Moreira, E. C. Costa, S. P. Miguel, and I. J. Correia, “Functionalization of AuMSS nanorods towards more effective cancer therapies,” *Nano Research*, vol. 12, no. 4, pp. 719–732, Jan. 2019, doi: https://doi.org/10.1007/s12274-019-2286-y.

[2] D. Rosenblum, N. Joshi, W. Tao, J. M. Karp, and D. Peer, “Progress and challenges towards targeted delivery of cancer therapeutics,” *Nature Communications*, vol. 9, no. 1, Apr. 2018, doi: https://doi.org/10.1038/s41467-018-03705-y.

[3] W. Sang, Z. Zhang, Y. Dai, and X. Chen, “Recent advances in nanomaterial-based synergistic combination cancer immunotherapy,” *Chemical Society Reviews*, vol. 48, no. 14, pp. 3771–3810, 2019, doi: https://doi.org/10.1039/c8cs00896e.

[4] A. F. Moreira, C. F. Rodrigues, T. A. Jacinto, S. P. Miguel, E. C. Costa, and I. J. Correia, “Microneedle-based delivery devices for cancer therapy: A review,” *Pharmacological Research*, vol. 148, p. 104438, Oct. 2019, doi: https://doi.org/10.1016/j.phrs.2019.104438.

[5] D. Li *et al.*, “Progress and perspective of microneedle system for anti-cancer drug delivery,” *Biomaterials*, vol. 264, p. 120410, Jan. 2021, doi: https://doi.org/10.1016/j.biomaterials.2020.120410.

[6] M. Wang, X. Li, W. Du, M. Sun, G. Ling, and P. Zhang, “Microneedle-mediated treatment for superficial tumors by combining multiple strategies,” *Drug Delivery and Translational Research*, Feb. 2023, doi: https://doi.org/10.1007/s13346-023-01297-9.

[7] L. Lin, L. Jiang, E. Ren, and G. Liu, “Bioorthogonal chemistry based on-demand drug delivery system in cancer therapy,” *Frontiers of Chemical Science and Engineering*, Jan. 2023, doi: https://doi.org/10.1007/s11705-022-2227-2.

[8] P. Khanna, J. A. Strom, J. I. Malone, and S. Bhansali, “Microneedle-Based Automated Therapy for Diabetes Mellitus,” *Journal of Diabetes Science and Technology*, vol. 2, no. 6, pp. 1122–1129, Nov. 2008, doi: https://doi.org/10.1177/193229680800200621.

[9] Y. Zhang, G. Jiang, W. Yu, D. Liu, and B. Xu, “Microneedles fabricated from alginate and maltose for transdermal delivery of insulin on diabetic rats,” *Materials Science and Engineering: C*, vol. 85, pp. 18–26, Apr. 2018, doi: https://doi.org/10.1016/j.msec.2017.12.006.

[10] Q. Zong, R. Guo, N. Dong, G. Ling, and P. Zhang, “Design and development of insulin microneedles for diabetes treatment,” *Drug Delivery and Translational Research*, Apr. 2021, doi: https://doi.org/10.1007/s13346-021-00981-y.

[11]A. H. Sabri *et al.*, "Expanding the applications of microneedles in dermatology," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 140, pp. 121–140, Jul. 2019, doi: https://doi.org/10.1016/j.ejpb.2019.05.001.

[12] M. Kirkby, A. R. J. Hutton, and R. F. Donnelly, "Microneedle Mediated Transdermal Delivery of Protein, Peptide and Antibody Based Therapeutics: Current Status and Future Considerations," *Pharmaceutical Research*, vol. 37, no. 6, Jun. 2020, doi: https://doi.org/10.1007/s11095-020-02844-6.

[13] F. Smith *et al.*, "The clinical and translational prospects of microneedle devices, with a focus on insulin therapy for diabetes mellitus as a case study," *International Journal of Pharmaceutics*, vol. 628, p. 122234, Nov. 2022, doi: https://doi.org/10.1016/j.ijpharm.2022.122234.

[14] P. Wang *et al.*, "Intelligent microneedle patch with prolonged local release of hydrogen and magnesium ions for diabetic wound healing," *Bioactive Materials*, vol. 24, pp. 463–476, Jun. 2023, doi: https://doi.org/10.1016/j.bioactmat.2023.01.001.

[15] H. Yuk, C.E. Varela, C.S. Nabzdyk, X. Mao, R.F. Padera, E.T. Roche, X. Zhao, Dry double-sided tape for adhesion of wet tissues and devices, Nature 575 (7781) (2019) 169–174.

[16] L.A. George, S.K. Sullivan, A. Giermasz, J.E.J. Rasko, B.J. Samelson-Jones, J. Ducore, A. Cuker, L.M. Sullivan, S. Majumdar, J. Teitel, C.E. McGuinn, M. V. Ragni, A.Y. Luk, D. Hui, J.F. Wright, Y. Chen, Y. Liu, K. Wachtel, A. Winters, S. Tiefenbacher, V.R. Arruda, J.C.M. van der Loo, O. Zelenaia, D. Takefman, M. E. Carr, L.B. Couto, X.M. Anguela, K.A. High, Hemophilia B gene therapy with a high-specific-activity factor IX variant, New Engl. J. Med. 377 (23) (2017) 2215–2227.

[17] R.H. Dong, C.C. Qin, X. Qiu, X. Yan, M. Yu, L. Cui, Y. Zhou, H.D. Zhang, X.Y. Jiang, Y.Z. Long, In situ precision electrospinning as an effective delivery technique for cyanoacrylate medical glue with high efficiency and low toxicity, Nanoscale 7 (46) (2015) 19468–19475.

[18] X. Zhang, G. Chen, L. Cai, Y. Wang, L. Sun, and Y. Zhao, "Bioinspired pagoda-like microneedle patches with strong fixation and hemostasis capabilities," *Chemical Engineering Journal*, vol. 414, p. 128905, Jun. 2021, doi: https://doi.org/10.1016/j.cej.2021.128905.

[19] J. Lv *et al.*, "Bilayer microneedles based on Bletilla striata polysaccharide containing asiaticoside effectively promote scarless wound healing," *Materials & Design*, vol. 226, p. 111655, Feb. 2023, doi: https://doi.org/10.1016/j.matdes.2023.111655.

[20] L. Long, D. Ji, C. Hu, L. Yang, S. Tang, and Y. Wang, "Microneedles for in situ tissue regeneration," *Materials Today Bio*, vol. 19, p. 100579, Apr. 2023, doi: https://doi.org/10.1016/j.mtbio.2023.100579.

[21] K. S. Yadav, R. Rajpurohit, and S. Sharma, "Glaucoma: Current treatment and impact of advanced drug delivery systems," *Life Sciences*, vol. 221, pp. 362–376, Mar. 2019, doi: https://doi.org/10.1016/j.lfs.2019.02.029.

[22] P. Gupta and K. S. Yadav, "Applications of microneedles in delivering drugs for various ocular diseases," *Life Sciences*, vol. 237, p. 116907, Nov. 2019, doi: https://doi.org/10.1016/j.lfs.2019.116907.

[23] A. Sheng *et al.*, "Micro/nanodevices for assessment and treatment in stomatology and ophthalmology," *Microsystems & Nanoengineering*, vol. 7, no. 1, pp. 1–19, Jan. 2021, doi: https://doi.org/10.1038/s41378-021-00238-1.

[24] A. Panda, V. A. Matadh, S. Suresh, H. N. Shivakumar, and S. N. Murthy, "Non-dermal applications of microneedle drug delivery systems," *Drug Delivery and Translational Research*, Feb. 2021, doi: https://doi.org/10.1007/s13346-021-00922-9.