International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Review on: Nanoneedle Based Intracellular Delivery of Drugs & Other Biomolecules

Amimul Ahasan[1], Md. Shahidul Islam*[2]
[1, 2]Department of Pharmacy, University of Science and Technology Chittagong (USTC), Chattogram, Bangladesh.

Abstract— *Nanoneedle is widely used nowadays to deliver drugs specially which contains nanoparticles. Besides, nanoneedle is also used to deliver probes, genes, proteins, DNA, RNA, peptides, vaccines etc. The delivery of drugs & biomolecules into living cells can provided by a nanoneedle with high spatiotemporal resolution, minimal damage. Thus, it become painless and noninvasive. Accessing the interior of live cells with minimal intrusiveness for visualizing, probing, and interrogating biological processes has been the ultimate goal of much of the biological experimental development. Current aim of research is to summarize the types, vehicles, materials, fabrication, advantages & future developments of nanoneedles. To serve the knowledge about recent development of nanoneedle based intracellular delivery. To review the wide applications of this new nanotechnology-based tool in the biological field, especially on its use for high-resolution studies of biological processes in living cells. All of the articles have searched from previous four months (April, 2020-July, 2020) and this articles are searched from various database including PubMed, MEDLINE, Sci-hub, Google scholar, THE LANCET etc. In this review, several important topic are discussed based on nanoneedles. These are:Nanoneedle based drug delivery vehicles, Material composition of nanoneedles, Nanoneedle arrays for intracellular delivery, Nanoneedle based drug delivery system, and Application of nanoneedle based delivery, Future Development nanoneedle based drug delivery. This study provides a comparative analysis of intracellular delivery using nanoneedles. Nanoneedles as new class of nanomaterial can influence molecular or cellular delivery of drugs & other biomolecules. Overall, this study identified key operating parameters and determined their effects on intracellular delivery and cell viability due to cell puncture using nanoneedles.*

Keywords— *Nanoneedle, Review, Biomolecules, Intracellular delivery.*

I. INTRODUCTION

The interface of nanotechnology and biology, or nano biotechnology, has brought in new opportunities and generated exciting development recently. With their high-aspect ratio, nanoscale geometry and excellent mechanical, electrical, and chemical properties, one-dimensional nanostructures, such as nanotubes and nanowires, play an important role in biology (1). For instance, carbon nanotubes have been explored as biosensors, membrane-penetrating delivery systems, and bio-imaging agents. In addition, such needlelike nanostructures can be mechanically manipulated to penetrate into living cells with minimal invasiveness, physically interconnecting intracellular environments to the outside of the cells. Conventional tools for manipulating cells and biomolecules, including optical tweezers, magnetic tweezers, atomic force microscopes, and micropipettes, are mostly limited to use for studies on cell membranes or outside of cells because of the difficulty in accessing the interior of cells with such tools (2). The unique ability of nanoneedles to access the interior of living cells can open up new opportunities to probe and manipulate biological processes and biophysical properties in living cells. For example, a nanoneedle functionalized with biomolecular species via cleavable linker molecules can be used to directly deliver the biomolecular species into a living cell over the cell membrane (3). A conductive nanoneedle electrically insulated with a thin layer of polymers, except the very end of its tip that serves as a nanoelectrode, can be used as a nanoscale electrochemical probe to measure electrochemical reactions and signaling processes occurring inside living cells or in the cellular network. Additionally, the small diameter and high-aspect ratio structure of the nanoneedle provides a nanoscale surface accessible for surface functionalization with numerous surface chemistry methods and a nanoscale carrier that can be physically manipulated with nanopositioning tools (4). This unique combination can enable targeted delivery of chemically unmodified species into microenvironments and even organelles in living cells and thus realize many new strategies to investigate biological mechanisms of living cells that are otherwise technically challenging or impossible to achieve with existing techniques (5).Here we discuss the recent progress in the development and application of one-dimensional needle-like nanostructures, or nanoneedles, for biological studies in living cells. We focus on the use of individual nanoneedles as nanoprobes for single-cell experiments, rather than the use of an array of nanoneedles fixed on the substrate. Several research groups have been developing the basic platform of nanoneedle technology for living cell experiments; however, the full potential of this emerging technology for studying fundamental biological problems remains to be realized (6).

II. MATERIALS AND METHODS

Research Protocol

International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Approximately **180** articles are screened for the evaluation of the review.

↓

Full text **60** articles are evaluated for eligibility for the review.

↓

I have searched all of the articles from **previous two months** and this articles are searched from various database including **PubMed**, **MEDLINE**, **Sci-hub**, **Google scholar, THE LANCET** etc.
1. MEDLINE (PubMed including Medline) (www.nlm.nih.gov/bsd/medline.html) - Medical Literature Analysis and Retrieval System Online.
2. Google Scholar
(https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=microneedle+based+drug+delivery+systems&oq=microneedle+bas)
The electronic resource and database are investigated for this systematic review for relevant population-based prevalence research from **last 10 years**.

In this review, It has been summarized the different types of nanoneedles, nanoneedle based intracellular delivery vehicles, materials composition of nanoneedles, nanoneedle arrays for intracellular delivery, and advantages of nanoneedles & future developments of nanoneedles. It has been served the knowledge about recent development of nanoneedles and use of the bio functionalized nanoneedles for local and spatially controlled intracellular delivery. It has been also reviewed the wide applications of this new nanotechnology-based tool in the biological field, especially on its use for high-resolution studies of biological processes in living cells.

III. Result and Discussion

After reviewing several literature on nanoneedle based intracellular delivery, It can say that nanoneedle is widely used nowadays to deliver drugs specially which contains nanoparticles. Besides, nanoneedle is also used to deliver probes, genes, proteins, DNA, RNA, peptides, vaccines etc.

In this review, It has been discussed several important topic based on nanoneedles. These are:

- Nanoneedle based drug delivery vehicles.
- Material composition of nanoneedles.
- Nanoneedle arrays for intracellular delivery.
- Nanoneedle based drug delivery system.
- Application of nanoneedle based delivery.
- Future Development nanoneedle based drug delivery.

Nanoparticles have either amorphous or crystalline solid property. Generally, they have made up of single component and exist in the size of about 5 - 200 nm. They have ability to absorb and (or) encapsulate drugs, so protecting them against chemical and enzymatic degradation. In relation to their role in controlled drug delivery, they have emerged as potential drug delivery systems (7). They have particularly employed in targeting particular tissues or organs as carriers of DNA in gene-therapy, and in their ability to deliver proteins, peptides, and genes through oral route. Efforts have made for applications of protein nanoparticles in drug delivery.Super paramagnetic iron oxide nanoparticles (SPIONs) were generally produce by reduction of the amount of iron salts under the alkaline conditions. They have assured to be promising drug delivery vehicles for some biomedical applications like targeted drug delivery and imaging, hyperthermia, magneto-transfections, gene therapy, stem cell tracing, molecular or cellular tracking, magnetic separation technology (e.g. rapid DNA sequencing),and detection of liver and lymph node metastases. In modern development, SPION have used successfully in order to quickly detect inflammatory diseases, cancer, diabetes and atherosclerosis (8). Currently, polyethylene glycol polyhedral oligo silsesquioxane (PEG-POSS) amphiphilic nanoparticles investigated to encapsulate insulin as new drug delivery vehicles. The research of insulin release have shown that PEG-POSS nanoparticles have used to protect insulin inside at gastric pH for two hrs.' and it was released at intestinal pH (pH 6 - 7), which is necessary for its absorption and activation (9). Nano cantilevers are consisting of flexible beams of carbon atoms. Like the lines of the diving boards, their beams have anchored with one end. The beams of Nano cantilever deflect when the biomolecules of interest bind. The deflections canfound by a laser light or by creating visual shifts in the physical properties of beams such as resonant-vibration frequencies. Therefore, these bio-molecular sensors have a large amount of "multiplex" functionality that is, to find a large number of different molecular species at the same time. In this way, nano cantilevers (like microscopic cantilevers) have developed for serum and tissue proteomics-based cancer diagnostics, prognostics and diagnostic-efficiency monitoring (10).

Nanopores are small holes designed in the particle. The pores are so small that even DNAmolecules can pass through them as one strand at a time, allowing accurate and specific DNAsequencing. Drug manufacturers can designnanopores into the surface of a drug capsule, which are only slightly larger than the drug's molecular size, therefore regulating the rate of diffusion of drug in the body. Currently, nanoporous systems engineered to mimic natural filtration systems, actively developed for use in smart implantable drug delivery systems, bio artificial organs, and other novel nano-enabled medical devices. Syntheticnanoporous element have many effective biological and medical applications including sorting, sensing, isolating, and releasing biological molecules (11). Researcher have applied nanopores with mesoporousthin silica films as anticancer drug carriers and attained mechanistic insights into the feasibility of using such films for drug delivery at the target-site (12).

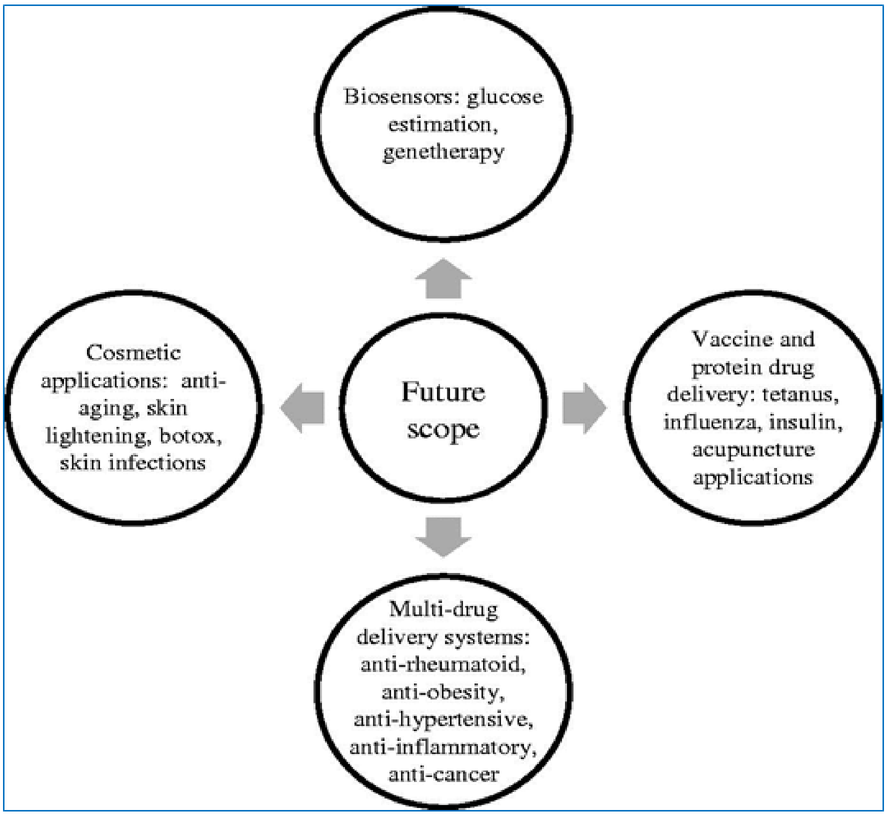
In this context, ultrafine needles provide less invasive means for molecular delivery, manipulating cells, and transmitting genes to living cells using atomic force microscope. The covalent bonding and affinity binding can used to immobilize DNA on the surface of nanoneedles. This method enables accurate displacement and low invasiveness. Recent studies have shown that chemically modified carbon nanotubes acts as nanoneedles and can easily pass through biological barriers and penetrating a wide range of cell types (13). This researcher reveals the efficacy of systemized carbon nanotubes as a new configuration of direct drug delivery. These systemized nanotubes able to act as cell-penetrating substances and can act as nanoneedlesthat pierce plasma membranes and translocate directly into cytoplasm without causing any cell damage and with the advantage of readily excreted. The nanotubes have structural advantages in which they are very thin but are too long, to offer a large surface area to which the necessary drug can bound. The large surface area allows the amount of drug loaded on nanotubes to regulate. Current researches directed to the study of improved efficiency of drug delivery and drug targeting, superior release profiles, and the study of reversible associations for the intracellular release of the drug (14).Oncology therapy, on the other hand, involves synthetic nanoneedles, which are highly custom-made ion channels that control the entire molecular movement across the cell membrane, targeting specific diseased cells. Recently, using quantum chemical calculations electronic and theoretical properties of ultrathin carbon and nitrogen needle-like and tube-like nanostructures, which are tighter than the smallest single wall nanotubes, have studied. However, although the preparation of this structure is not relatively simple, the objective of study was to interpret the geometry and stability of the family of the packed carbonnanoneedles (CNNS) using the Quantum Chemistry Computational Modeling Method (15).

Future Development Nenoneedle Based Drug Delivery

The microarray drug delivery system has gained immense success in therapeutics, and has paved the way for the use of a more efficient and novel transdermal delivery route. Nanoneedles, on the other hand, are under research, and have immense potential to be used in various applications such as vaccine delivery, diabetes management, cancer therapy, gene therapy and antihypertensive therapy. This system can be used for multidrug delivery, protein drug delivery, in skin diseases such as psoriasis, anti-inflammatory treatment and hormone therapy. The future of therapeutics thus involves a wide application of the novel nanoneedle system in the delivery of a wide range of drugs across the skin barrier efficiently, thus revolutionizing transdermal delivery. Nanoneedles in the future have immense applications and scope in the field of biosensors. They can be used in electronics, as electrodes, where the nanoneedles in contact with skin act as a sensor device to send signals, which can be utilized, to make watches that work on body stimuli. Nanoneedles can also be used in formulation of pulsatile drug delivery, and thus drug release can be modulated according to the specific needs. This also paves the way for modulation of drug release using electrodes

Since nanoneedles have such a wide array of applications, it is highly likely that they will positively impact many key industries in the future. The precise nature of nanoneedles means that they are likely to find some use in drug delivery directly to *specific* tissues or even cells in a human body. For example, cytotoxic drugs can be specifically delivered to cancerous tissues/cells so as to kill them without damaging the cells around them. Currently, most treatment damages the healthy cells around the damaged ones, therefore are not optimal means of treatment. With nanoneedles, we can accurately target them without damaging the cells around them, therefore nanoneedles could be an effective mean of treatment in the future (16).

Furthermore, nanoneedles could replace the need for injection. With the use of nanoneedles, it is possible to deliver drugs by applying it to the skin of the patient. Nanoneedles act as a cargo which will pass through the epidermis and directly into the bloodstream, hence replacing injections and allowing patients to have a pain free treatment. This would be an effective advancement especially with smaller children who are scared of injections. By allowing a pain free treatment, children will be more willing to undergo treatment and will have better experience during the treatment. This would also make children be more willing to inform parents if they are ill as they will be less afraid of doctors.



Alternatively, cargo other than drugs can be delivered to cells so as to force them to undergo certain processes. DNA/RNA sequences or proteins could be delivered to cells to give them certain functions and signaling molecules to trigger certain mechanisms in cells. Cancer cells usually are results from cellular mutations during cell division, therefore with nanoneedles, it would be possible to activate the termination sequence, and thus nipping the bud before it takes root. Another possibility would be that nanoneedles could speed up the process of certain process such as cell division. This would help patients which suffer from lower blood or platelet count as it will speed up the rate of cell division, thus returning them back to normal count. This would be better than blood transfusion as the cells are of the original not of some stranger. In addition, this would reduce the pressure on the blood banks as help them focus on those who need it more. Furthermore, this would eliminate the chances of contacting other viruses during the transfusion, thus making it a more reliable method (17).

IV. Conclusion

This study provides a comparative analysis of intracellular delivery using nanoneedles. It has been summarized how nanoneedles as new class of nanomaterial can influence molecular or cellular delivery of drugs. Nanoneedles can also be used to deliver molecules such as nucleic acids, proteins, or other chemicals to the nucleus, or may even be used to carry out cell surgery. Using the nanoneedle approach, we can get to a very specific location within the nucleus; this is the key advantage of this method. Overall, this study identified key operating parameters and determined their effects on intracellular delivery and cell viability due to cell puncture using nanoneedles. Finally, we envision nanoneedles working hand-in-hand with nanorobots; the specificity of the nanoneedles would allow delivery of these multifunctional machines straight into specific cells and allow them to do their work without fear of side effects.

References

[1] Kolahalam, L. A., KasiViswanath, I. V., Diwakar, B. S., Govindh, B., Reddy, V., & Murthy, Y. L. N. (2019). Review on nanomaterials: Synthesis and applications. Materials Today: Proceedings.
[2] B.S. Wakure, N.M. Bhatia. A review on nanoneedle- A smart nanovector for drug delivery. World J Pharm Sci 2017; 5(7): 101-110.
[3] Shende P, Sardesai M, Gaud RS. Micro to nanoneedles: a trend of modernized transepidermal drug delivery system. Artificial cells, nanomedicine, and biotechnology. 2018 Jan 2;46(1):19-25.
[4] Chiappini C, Martinez JO, De Rosa E, Almeida CS, Tasciotti E, Stevens MM. Biodegradable nanoneedles for localized delivery of nanoparticles in vivo: exploring the biointerface. ACS nano. 2015 May 26;9(5):5500-9.
[5] Matsumoto D, Yamagishi A, Saito M, Sathuluri RR, Silberberg YR, Iwata F, Kobayashi T, Nakamura C. Mechanoporation of living cells for delivery of macromolecules using nanoneedle array. Journal of bioscience and bioengineering. 2016 Dec 1;122(6):748-52.
[6] Han SW, Nakamura C, Obataya I, Nakamura N, Miyake J. A molecular delivery system by using AFM and nanoneedle. Biosensors and Bioelectronics. 2005 Apr 15;20(10):2120-5.
[7] Kolhar P, Doshi N, Mitragotri S. Polymer Nanoneedle- Mediated Intracellular Drug Delivery. Small. 2011 Jul 18;7(14):2094-100.
[8] Matsumoto D, Sathuluri RR, Kato Y, Silberberg YR, Kawamura R, Iwata F, Kobayashi T, Nakamura C. Oscillating high-aspect-ratio monolithic silicon nanoneedle array enables efficient delivery of functional bio-macromolecules into living cells. Scientific reports. 2015 Oct 16;5(1):1-9.

[9] Jahanshahi M, Babaei Z. Protein nanoparticle: A unique system as drug delivery vehicles. African Journal of Biotechnology2008;7(25):4926-34.
[10] Sharma HS et al. Nano wired-Drug Delivery Enhances Neuroprotective Efficacy of Compounds and Reduces Spinal CordEdema Formation and Improves Functional Outcome Following Spinal Cord Injury in the Rat. In: Acta Neurochir Supplement 2010; 343-50.
[11] Shalek AK, Robinson JT, Karp ES, Lee JS, Ahn DR, Yoon MH, Sutton A, Jorgolli M, Gertner RS, Gujral TS, MacBeath G. Vertical silicon nanowires as a universal platform for delivering biomolecules into living cells. Proceedings of the National Academy of Sciences. 2010 Feb 2;107(5):1870-5.
[12] Shalek AK, Gaublomme JT, Wang L, Yosef N, Chevrier N, Andersen MS, Robinson JT, Pochet N, Neuberg D, Gertner RS, Amit I. Nanowire-mediated delivery enables functional interrogation of primary immune cells: application to the analysis of chronic lymphocytic leukemia. Nano letters. 2012 Dec 12;12(12):6498-504.
[13] Shalek AK, Gaublomme JT, Wang L, Yosef N, Chevrier N, Andersen MS, Robinson JT, Pochet N, Neuberg D, Gertner RS, Amit I. Nanowire-mediated delivery enables functional interrogation of primary immune cells: application to the analysis of chronic lymphocytic leukemia. Nano letters. 2012 Dec 12;12(12):6498-504.
[14] Chiappini C, De Rosa E, Martinez JO, Liu X, Steele J, Stevens MM, Tasciotti E. Biodegradable silicon nanoneedles delivering nucleic acids intracellularly induce localized in vivo neovascularization. Nature materials. 2015 May;14(5):532-9.
[15] Kim W, Ng JK, Kunitake ME, Conklin BR, Yang P. Interfacing silicon nanowires with mammalian cells. Journal of the American Chemical Society. 2007 Jun 13;129(23):7228-9.
[16] Park S, Choi SO, Paik SJ, Choi S, Allen M, Prausnitz M. Intracellular delivery of molecules using microfabricated nanoneedle arrays. Biomedical microdevices. 2016 Feb 1;18(1):10.
[17] Han SW, Nakamura C, Obataya I, Nakamura N, Miyake J. A molecular delivery system by using AFM and nanoneedle. Biosensors and Bioelectronics. 2005 Apr 15;20(10):2120-5.

*For Correspondence: Md. Shahidul Islam, Assistant Professor, Department of Pharmacy, University of Science & Technology Chittagong (USTC).