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REVIEW ARTICLE **OPEN ACCESS**

Gene-specific drug delivery system: An art of war

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ABSTRACT

Drug delivery key research aim is to support patients by designing clinically effective formulations. Drug delivery systems can enhance the treatment of a variety of diseases, including microbes' infections, and cancers. Drug delivery systems preparation methods, on the other hand, remain difficult, particularly at the microscale. Some of the necessary criteria for speeding the transformation of drug delivery systems from a limited scale to an enormous scale include reducing batch-to-batch variance and increasing production volume. Gene-specific drug delivery system has a bright future as a preventive solution to severe diseases and has developed as an influential tool in recent years as a unique technology for disease management. Gene silencing, protein expression, or gene repair may be used to cure perhaps every illness with a gene-specific delivery system. The genetic material must be paired with a delivery additive to successfully transfer the nucleic acid payload to its target tissue. There are various non-viral and viral vectors involved along with the different mechanisms of gene entry into a cell which is discussed in this article. This review highlights that the gene-specific drug delivery system has vast scope in therapy and can prove advantageous over other therapies, and includes several carriers and different methods of plasma membrane permeation. Very interestingly, it also includes various applications of the gene-specific drug delivery system in several diseases and recent trends in the Coronavirus vaccine.

Keywords: *Viral, Non-viral vectors, Chitosan, Cancer, Dendrimers, COVID-19, Transfection.*

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INTRODUCTION

Gene therapy is a means of treating or avoiding illness by modifying the genes within the body's cells. Genes that aren't functioning correctly could be to blame for the disorder. By deleting a faulty gene or introducing a new gene, gene therapy seeks to cure disease or enhance the body's ability to battle illness. Among other disorders, gene therapy carries the potential for the treatment of tumors, cystic fibrosis, cardiovascular disease, obesity, and hemophilia.Gene therapy works either by substituting transformed genes or anchoring transformed genes. Thereby increasing the visibility of infected cells to the body's defense system. Summing it up, the endogenous genome is manipulated.

One of the problems related to gene-specific treatment is that the gene cannot be specifically imbibed into the cell's nucleus. It requires a transporter or a conveyer (a vector).Viruses have the property to recognize particular cells and pass DNA/RNA into the cells' total sets of genes due to which they are mainly used as carriers. The infected gene is replaced with the gene of interest in the virus.

When administered encapsulated or conjugated to the surface of nanoparticles, gene silencing therapeutics, siRNAs, have been shown to have slightly longer half-lives. In certain cases, these therapeutics are used to treat 'undruggable' cancer proteins. Furthermore, it has been shown that the improved stability of genetic therapies provided by nanocarriers, which is also paired with controlled release, prolongs their effects [1].One of the challenges faced in gene therapy is delivering the gene to the right place and switching it on. As a consequence, gene therapy often necessitates a case-by-case approach. This could be beneficial, but it could also be very costly [2].In today's drug treatment, vast patient populations are treated as individuals, regardless of the possibility of human, genetically dependent variations in drug reaction. Pharmacogenomics, on the other hand, could be able to better target successful treatment on smaller patient subpopulations that, though sharing the same disease phenotype, have different genetic profiles. It's also uncertain if this plan would result in successful, more cost-effective care [3,4,5].

Plasmids with the fundamental constituents of gene expression

One of the keys to effective gene therapy is selecting the best vector. There are several different types of vectors, both viral and non-viral, and the most widely used ones are mentioned below.

VIRAL VECTORS: In order to improve protection, uptake, and performance, there has been a renovation in the viral carriers for them to be utilized in gene-specific delivery. The vectors can be said to be of two types based on their cell entrance, one which enters the cell's nucleus and the other which stays in the cytoplasm to show action. These vectors or carriers are obtained from deoxyribonucleic acid or ribonucleic acid [6].Viral vectors are broadly divided on the basis of the derivative host as represented in figure 1.In a perfect scenario, the viral carriers that show implementations in gene-specific drug delivery show benefits of the relatively sophisticated viral infection mechanism whilst also escaping the pronouncement of an infected part that results in viral multiplication and fatal effect in a person who's being exposed [7].

There are 5 major types of clinically effective viral vectors currently known:

Retroviral vectors: In gene therapy, retroviruses are one of the most commonly used viral vectors. During their life cycle, they integrate their complementary DNA into the host genome, resulting in faithful transgene transmission into the transduced cell progeny[8].

AAV: Among the most widely studied gene therapy engines is adeno-associated virus (AAV). It was first found in adenovirus formulations as a contaminant. Recombinant AAV (rAAV), which lacks viral DNA, is a protein-based nanoparticle intended to cross the cell membrane and carry the DNA cargo to the cell's nucleus [9].

Bacteriophage: Despite the fact that natural bacteriophages are prokaryotic viruses, some experiments have shown that phage can be modified to carry genes to mammalian cells. Because of their versatility and ease of manipulation and development, they have applications in biotechnology and medicine for testing, therapeutics, and manufacture [10].

The general properties of the viral carriers such as their merits, demerits, size, families are mentioned in the above table 1.

NON-VIRAL VECTORS: Non-viral nucleic acid carriers are used to transport genes to various cells and groups of cells. Non-viral vectors show properties like easier to pick out, safe to stockpile, found to be copious, and can possibly be frequently given showing limited defense by the body to it [11].

The bulk of non-viral carriers show characteristics of positively charged DNA/RNA condensation. Centered on nature, these vectors are divided into two sets as represented in Figure 2.

Natural or Synthetic: Naturally degradable positively charged ions are studied extensively due to their low toxicity in the body. In the majority of these carriers positively charged proteins, lipids chains of monomers, or combinations of these are used [12].

Methods for using polymers as gene carriers:

- DNA/RNA condensation
- Direct form of conjugation

The structures of various polymers used as natural or synthetic, naturally degrading carriers are shown in figure 3.

Polyethyleneimine: It is a positively charged (cationic) polymer that commonly shows its application in the transmission of the gene of interest. Because of the skills to transport huge amounts of genes, showing adaptable output, these cationic carriers are perfect contestants for DNA/RNA delivery [13]. PEI can have both branched (BPEI) and liner (LPEI). In salt-containing conditions, branched PEIs are highly reactive and seem to conjugate with DNA. Linear PEIs are comparatively showing decreased toxicity and an elevated carrier performance capacity [14].A CIJ which is a unit confined impinging jet mixer was applied under fast mixing conditions to manufacture nanoparticles that were complex type polyelectrolyte. Prior to processing, each stream is filled separately containing the polyethyleneimine or the gene nanoparticles and put inside a tiny chamber [15]. Since native PEI is non-degradable, it has a poor clearance rate in the systemic circulation. As a result, several studies have centered on the progress of naturally degradable PEI [16]. The delivery assisted by PEI can perhaps result as a potential treatment option in curing disorders that require an amalgam of chemotherapy and DNA therapy [13].

Chitosan: Chitosan is one of the most commonly used cationic polymers due to its potential to release incorporated drugs for a longer duration of time. For the preparation of Chitosan/DNA nanospheres, a unique and easy osmosis-linked process was patented [17]. The DNA integration was relatively large (up to 30%) using this approach, as it's a laborious, and slow process of liberation. Several formulation parameters influence transfection performance, including salt type, molecular weight, acidity/basicity, N/P ratio, and so on. Taking into account all of the research, it seems various molecular weight values and DDA parameters that shape complexes with optimum stability and transfection efficiency [18]. To improve the complex's cell-penetrating capacity and endosomal release, octaarginine-modified chitosan (R8- CS) was synthesized [19]. Gene-specific DDS which includes a matrix mechanism having chitosan may be an exciting area of study, with growing usefulness in rejuvenating dosage forms. Works involving

stem cells are significant as the coated gene that monitors the seeded cells' dedifferentiation can elevate the signals at the implantation area [20].

Cationic block co polymers: Due to the potential to solely aggregate in solid form and having limited solvents, block co-polymers are fascinating polymeric materials [21]. Polyplexes are stable nanoparticles formed by the electrostatic reaction of the DNA (phosphate end) alongside cationic block co-polymers. PDMAEMA, shows the property of being biostable, pKa (7.4-7.5), water-dissolving while considering MW [21,22]. Being used as a non-viral DNA carrier it can be endocytosed into cells. Various factors like size of molecules, DNA attachment, buffer, form, affect the transfer of genes. DNA transfer, precipitation and attachment are all affected by the form and flexibility of the co-polymer. The capacity of this co-polymer of being able to coil on all sides of RNA/DNA resulting in a nice cast is improved by the linear chain and the mass generating unit of polymers [21].

Polymethacrylates: In both in vivo and in vitro model systems, polymethacrylate, a vinyl-based cationic polymer, has been used for gene delivery. The polymer has evolved to increase its biodegradability, gene distribution effectiveness, and toxicity. It was conjugated with a hydrolyzable cationic side chain to improve thepolymer's biodegradability [23]. PMMA has poor contact with the cell membrane, so it may need to be modified further to improve penetration. To improve transfection performance in a sample this polymer was mixed with a peptide which was cell pungent and soluble.

PLGA – Poly (lactic-co-glycolic acid): Of all possible vectors, PLGA has been regarded as one of the most potent candidates. It's a lactic and glycolic acid co-polymer that's connected by an ester bond. The DNA entrapment time in a polymer is affected by constituents of the polymer, its weight, size and morphological structure. Because of its effective cellular absorption, fast endosomal escape, and continuous release of the therapeutic molecule, a PLGA nanoparticle is useful in gene silencing [24]. The PEI-based PLGA formulation has been shown to have lower cytotoxicity and improved serum stability [25].

Dendrimers: Dendrimers may form complexes with genomic material such as RNA, plasmid DNA, and antisense oligonucleotides, among other things. They are artificial macromolecules with a compact molecular structure and a classification of different functional groups. Dendrimers have the ability to form polycations in a variety of physiological conditions, as well as the ability to bind genetic molecules with a negative charge and associate with nucleic acid anionic groups. Dendrimers with structurally tailored structures are used to increase delivery performance thus reducing cytotoxicity [26]. Figure 4, represents the various types of dendrimers broadly segregated. Dendrimer-based delivery mechanisms have shown a lot of promise as methods for improving genetic therapies. PAMAM dendrimers are undoubtedly among the best and most commonly used transfection agents, and many cells and molecular biologists use them as a basic method [27].

Inorganic nanoscopic particles: Inorganic nanoscopic particles are miniature showing both unique chemistry and physical nature vary according to particle size. Gold (Au) and Silver (Ag) are used to make inorganic nanoparticles, magnetic nanoparticles consisting of Nickel, Cobalt, Iron, and iron oxide that are superparamagnetic, have massive magnetic motion in the magnetic arena, and fluorescent nanoparticles including quantum dots and SiO2, for example [28].

Silica nanoparticles: Mesoporous silica nanoparticles (MSNs) are made from amorphous SiO2 in a matrix form along with mesoporous permeability. MSNs are an appealing choice of dosage form due to characteristics like texture, durability, uncomplicated changeability [29]. MSNs may have their surfaces changed to produce cationic molecules which bind to anionic nucleic acid. The second choice which leads to MSNs being a reasonable method for gene transfer includes covering these with positively charged portion, while the inside includes an anionic nucleic acid that's injected for travel. These are favorable candidates as co-delivery units.in animal studies, great therapeutic effectiveness can be demonstrated by deliberately picking all units which are to be bombarded into the site of interest and other structures. The successive move is to choose the best formula, optimize it for the mass manufacturing process, which leads to evaluation tests in patient applicable models, finally implementation in human trials [30].

Gold nanoparticles (GNPs): Through the use of cationic co-carriers, GNPs containing synthetic microRNAs can invade cells [31]. GNPs–microRNA conjugation is a novel method for microRNA delivery that could be used in a microRNA replacement scheme [32]. Ground operation of GNP, amino acids cause the genes to condense on the membrane. Powerful uptake and lower body defense have been demonstrated in DNA and gold nanoscopic particles, which are changed by an oligonucleotide [33]. Using folic acid (FA)-based ligands, large transportability of the gene (80-90%) was obtained for GNPs which were surfaced by lipids in MCF-7 type of cell [34].

Magnetic nanoparticles (MNPs): Magnetic nanoparticles are a kind of nanoparticle that can be controlled by applying magnetic fields to them. A magnetic material, such as iron, nickel, or cobalt, and a chemical component with usability, often with (bio)catalytic or biorecognition properties, are typical

components of such particles. The use of magnetic nanoparticles is seen in gene cloning, RNA/DNA purification [35]. MNPs serve as monitors, evaluating the state of the disorder and dispensing medications to cure it. Their high charge adds to their stabilization by avoiding particle precipitation and settling due to gravitational forces [36].

Carbon nanotubes (CNTs): Carbon nanotubes (CNTs) are carbon tubes with nanometer-sized diameters. Of all nanomaterials, carbon nanotubes have the largest surface area for chemical alteration. The use of nanotubes as a carrier for gene silencing has been shown to be effective in slowing the growth of cancer cells. CNTs creation for implementation as a carrier, non-viral type in genetic drug delivery, the bits of advice are:

- Physical characteristic adjustment although difficult must be ticked while developing DNA payload. While increasing bioavailability and decreasing the harmfulness of the CNT, the electric structural feature should be modified.
- Engineering of the side chain groups during the preparation of naturally compatible nanotubes must be done while considering the solubility of the ultimate unit alongside. Modified CNTs need to show maximum payload while retaining stability throughout the process. Further study would allow for greater knowledge and regenerative forms of gene-specific drug delivery applications [37,38].

QD - Quantum dots: Nanoscopic lattice QDs can transport electrons and are made by humans. In recent years a number of techniques for DNA combination with QDs have been published, including electric, combined interaction, among others [38a,39,40]. mi RNA, tumor cell identification, single-stranded RNA delivery has all been shown to be successful with these higher-order assemblies [41].

Enhancing of gene drug delivery by Physical Methods: Advanced physical gene distribution techniques, such as sonoporation, electroporation, gene gun, magnetoporation, and optoporation, have been extensively developed and are gaining attraction due to their briefness and lack of toxicity.

Electroporation: The physical process of inserting polar molecules such as DNA into eukaryotic cells via the cell membrane by exposing cells to electric pulses is known as electroporation or electropermeabilization (EP). Because of its high gene transmission quality and reduced side effects, electroporation is becoming more common as a nonviral gene delivery tool. It may transmit genes to a range of tissues, including muscle, skin, and even tumors specifically [42]. Despite the fact that electroporation has been extensively studied and applied, it is still constrained by the following limitations: (i)electroporation's transfection efficiency varies based on the tumor type, (ii) electroporation's cell viability is still poor [43].The process of electroporation is represented by figure 5.

Sonoporation: The term "sonoporation" refers to the use of ultrasound to create tiny openings in cell membranes for the transport of nucleic acid materials. Sonoporation is analogous to electroporation, in which DNA is propelled along an electromagnetic field by an electrical force. Passive diffusion is used to mediate sonoporation. The duration and strength of ultrasound determine the efficiency of the transition. When used in conjunction with therapeutic genes, sonoporation has the potential to induce apoptosis. The use of combinations with chemicals and diagnostic ultrasound are optimistic ways to address the current drawbacks of sonoporation, which include poor efficiency of gene transfer and disruption to target cells [44].This sonoporation process can be better understood by Figure 6.

Magnetoporation: The aim of magnetoporation is to bring genetic material into the cell while being influenced by a magnetic field A biomolecule/magnetic reagent composite is formed by mixing exogenous nucleic acids with magnetofection reagent. The composite is then transported into the cell under the influence of a magnetic field. The phagocytosis and pinocytosis of cell membranes were stimulated by the magnetic field [43].

Optoporation: Optoporation, a method for inserting specific genes into targeting cells that use directed laser pulses to create a temporary fracture in the plasma membrane, has been extended to a range of cell types in vitro. It has been discovered that when DNA plasmid is exposed to radiation with higher-energy, isolated pulses, it piles up on the cell membrane at the incinerated site. It has been discovered that when DNA plasmid is exposed to radiation with higher-energy, isolated pulses, it piles up on the cell membrane at the incinerated site [45].

Gene therapy in COVID-19 vaccine: Gene therapy in COVID-19 has implementation such as a multivalent vaccine which targets the coronavirus antisense Ribonucleic acid and a double-stranded ribonucleic acid which aims at the ORF1ab of SARS-CoV-2 and the N, E, S and M region of the genome were recently patented. Additionally, 2 single-stranded RNAs targeting the CoV-2 gene area which is conserved are created which together inhibited the SARS-CoV-2 gene significantly [46]. Pfizer, Moderna Inc. and BioNTech recently formulated vaccines mRNA-1273 and BNT162 were recently approved by the US FDA for emergency use and vaccination. This study covers the coronavirus related anatomy, methodology of the viral spreadability, methods of identification of viral strains, human manifestations [47].

IMPLEMENTATIONS

- AAV8 vector infusion results in strong Factor IX gene expression hence used to treat Hemophilia B [48].
- Platelet gene therapy for hemophilia A is made possible by nongenotoxic antibody-drug conjugate conditioning [49].
- Gene specific drug delivery system is used in treating Cystic Fibrosis [50,51].
- Parkinson's Disease is also treated using gene specific drug delivery [52].
- Huntington's disease is treated using gene specific drugs [53].
- Treating intrinsic error of metabolism, such as that of liver [54,55].
- In stomach cancer, MicroRNA-335-5p can act as a silencer of tumors and aggression [56].
- Using myeloid cell-specific gene promoters, hematopoietic stem cell gene delivery for brain metastases has been created [57].
- Tumor compressing genes are used for combination cancer therapy [58].
- m-RNA are delivered to specific tissues for more efficient outcomes [59].
- Some genes directed enzymes treatment can be used to treat cancers [60].
- To resolve numerous drug resistance and facilitate synergistic tumors inhibition, gene and chemotherapeutics are delivered simultaneously via co-polymeric micellar nanostructures [61].
- Nanostructure carrier lipids are used as gene specific drug delivery system in lung cancer [62].
- By targeting BTG2, MiR-27a-3p acts as an oncogene in gastric cancer [63].
- Cardiac remodeling in Type 2 diabetes, effect is suppressed due to gene therapy that targets cardiac p110α [64].
- Gliomas are also treated using gene therapy [65].
- Treatment of Niemann Picks type C2 disease with gene therapy to the blood–brain barrier and subsequent protein secretion [66].
- Using human HSC gene editing to dissect ELANE neutropenia pathogenicity [67].
- Preparing mRNA vaccines that self-assemble [68].
- Gene specific drug delivery as personalized medicine for neurological disorder [69].
- Crispr CAS9-based gene therapy for lung cancer is being developed [70].
- In sickle cell disorder, gene therapy will improve [71].
- Spinal Muscular Atrophy treatment Gene Therapy [72].
- The cells of hair are regenerated by using gene therapy [73].
- Neovascular Eye disease is also treated using gene specific drug delivery systems [74].
- Cancer immunotherapy is also carried out using gene therapy [75].
- Using a Cocal-Pseudotyped Lentiviral Vector, In Vivo Gene Therapy for Canine SCID-X1 [76].
- Applications in dermatology is also recently observed [77].
- There are gene specific drug delivery systems developed for the treatment of intervertebral disc degeneration [78].
- Gene therapy is also used in treating lysosomal storage diseases [79].
- Inner ear gene delivery using viral vectors [80].
- Glaucoma is also treated by gene therapy [81,82].
- AIEgen probes with peptide or DNA modifications for biosensing are built in a modular fashion [83].
- Tetrahedral self-assembled DNA nanostructures are formulated and used [84].
- GNPs are used for the viral detection [85].
- DNA sensors are being used for the detection of genes [86].
- Uveal melanoma hereditary prediction using gene therapy [10].
- 2D nanoparticles have been synthesized for gene therapy [87].
- Mitotic cycle of prostate cancer cells is inhibited by gene specific drugs [88].
- Neuromuscular drugs are treated using RNA-target drugs [89].
- Development is seen in ocular single stranded RNA targets and drug delivery systems [90].
- Gene therapy by CRISPR is now seeming to replace the antiviral drugs [91].
- Gene delivery is also carried out using Electro spun material [92].
- Gene biomarkers are used to target cancer cells [93].
- Cardiovascular diseases are treated using gene specific nanoparticles [94].
- Polypeptides that are elastin like are developed for *in vivo* specific gene therapy [95].
- Hepatocellular carcinoma was treated using RNA nanoparticles [96].
- In the treatment of Alport Syndrome, adenovirus carriers are used to pass DNA or RNA in the cells of

the glomerulus [97].

- COVID-19 Vaccines are being developed using gene-specific drug delivery system [98].

Table 1. General properties of Viral vectors

Vectors	**Retroviral**	**Adenoviral**	**AAV**
Family	*Retroviridae*	*Adenoviridae*	*Parvoviridae*
Particle size	80–100nm	80–100nm	20nm
Genome	ssRNA	dsDNA	dsDNA
Max. Transgene Capacity	12kb	36kb	5kb
Advantages	Safety is paramount. Integration of genes onto the genome. Immunogenicity is low.	Titers are large. Move transgene efficiently into both dividing and dormant cells.	The chromosome's integration. A vast array of hosts is available. Sustainability. Immunogenicity is low. Both actively dividing and quiescent cells are affected.
Disadvantages	Titer is low. Just works with cells that are actively dividing. Induction in insertional mutagenesis.	Immunogenic in nature. Transgene expression within a short period of time.	Packaging capability is restricted. Toxicity of stem cells is a probability.

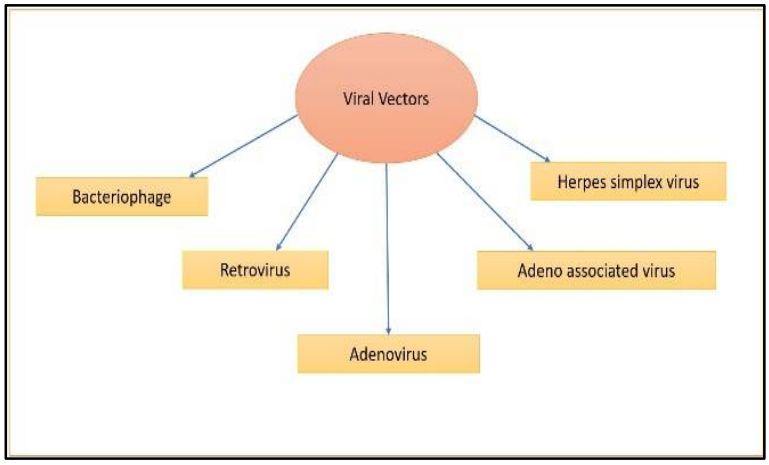

Figure 1. Types of Viral vectors

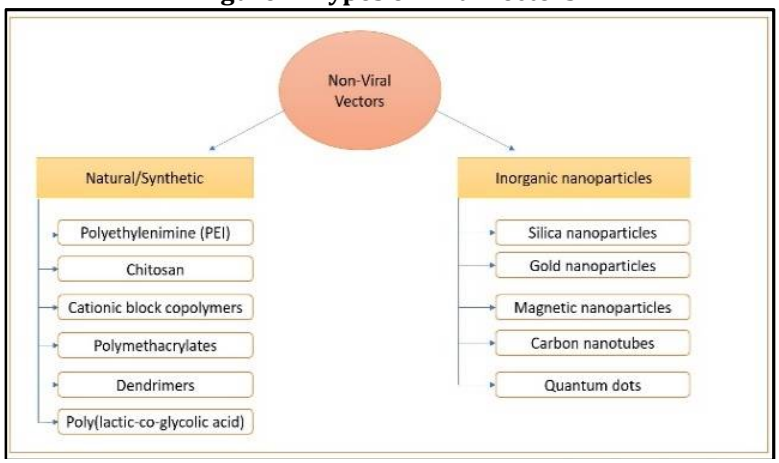

Figure 2. Classification of Non-Viral carriers

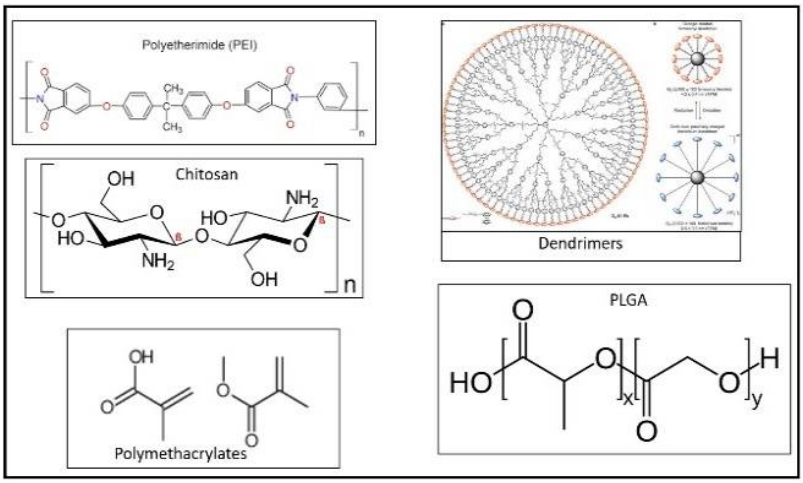

Figure 3. Natural or Synthetic Polymers

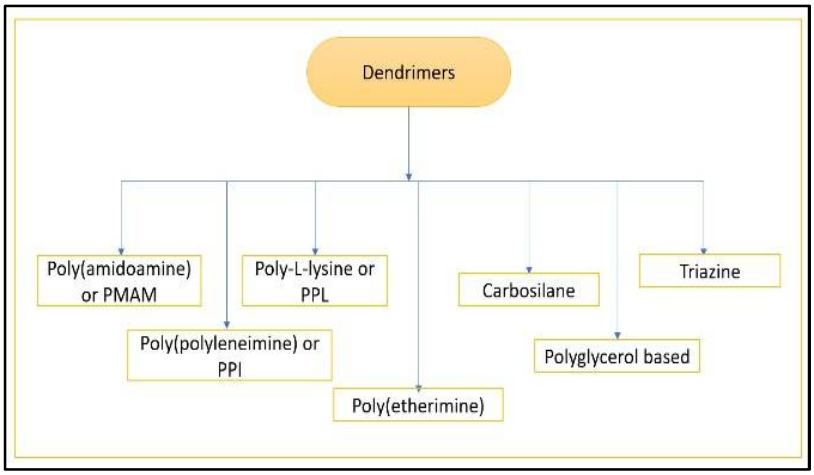

Figure 4. Types of Dendrimers

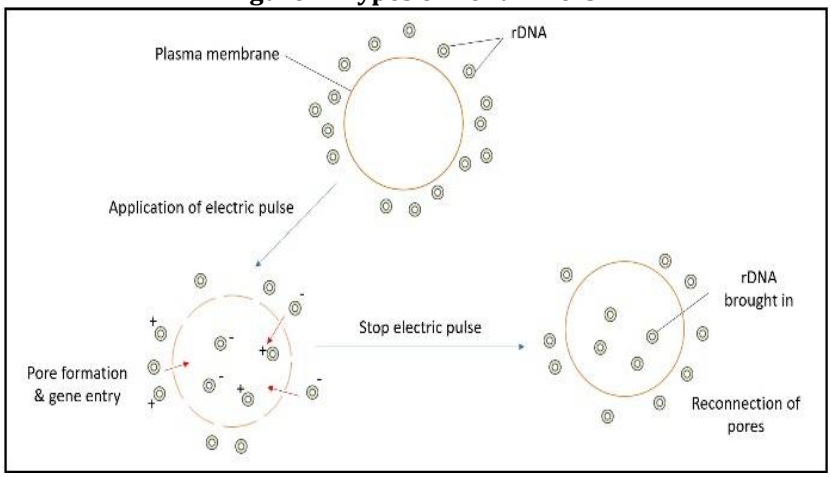

Figure 5. Electroporation

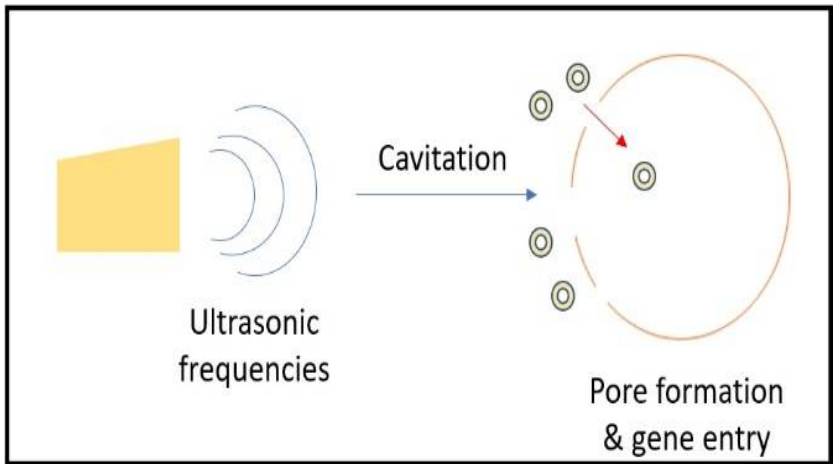

Figure 6. Sonoporation

CONCLUSION

The ability for gene therapy to have long-term health benefits, as shown by research advancements and clinical successes in recent years, justifies continued hope and increased attempts to make this therapy part of our regular armamentarium for treating severe human diseases. The progress made in discovering miRNA functions and their roles in cancer has sparked high hopes for a gene-specific drug delivery mechanism. Clinical gene therapy is based on delivering genetic information to tissues in vivo and is a popular procedure used in science. Gene-specific drug delivery system shows multiplied effectiveness, monitoring, drug availability, and distribution over other drug delivery systems.

To conclude, this review highlights that the gene-specific drug delivery system has vast scope in therapy and can prove advantageous over other therapies, and includes several carriers and different methods of plasma membrane permeation. All of these factors can be modified as per convenience to achieve better and desired results. Also, the article includes recent advancements and the role of gene delivery in COVID-19 vaccines.

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