Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

Deep view of Polyethylenimine polymer as a non-viral vector for gene therapy

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Abstract
Polyethylenimine (PEI) is a general-purpose polycationic polymer which has received much attention as a non-viral vector for therapeutic nucleic acid delivery in medicine. The high level of amine groups enables electrostatic complexation with negatively charged genetic material, leading to the formation of polyplex and higher cellular uptake. Once internalized, PEI can facilitate endosomal escape because of its buffering capacity and or its ability to destabilize cellular membranes, which promotes efficient delivery of DNA and RNA. Recent use of PEI-based systems for gene delivery (DNA and small interfering RNA) and other gene therapy and neurological applications are emphasized. The transfection efficiency is high, but clinical translation is hindered by its cytotoxicity and low biodegradability and systemic stability. Current strategies, namely molecular modification, crosslinking, surface shielding and structural optimization of PEI-based gene-delivery system are then explored for enhancing the safety and therapeutic promise of this platform. This review focuses on major forms of PEI, molecular structure, physicochemical properties influence gene-delivery performance and applications on non-viral gene delivery.

Keywords: Polyethylenimine (PEI), Internalization, Non-viral gene delivery, Proton sponge, Polyplex nanoparticles, Transfection, Cytotoxicity.

1. Introduction

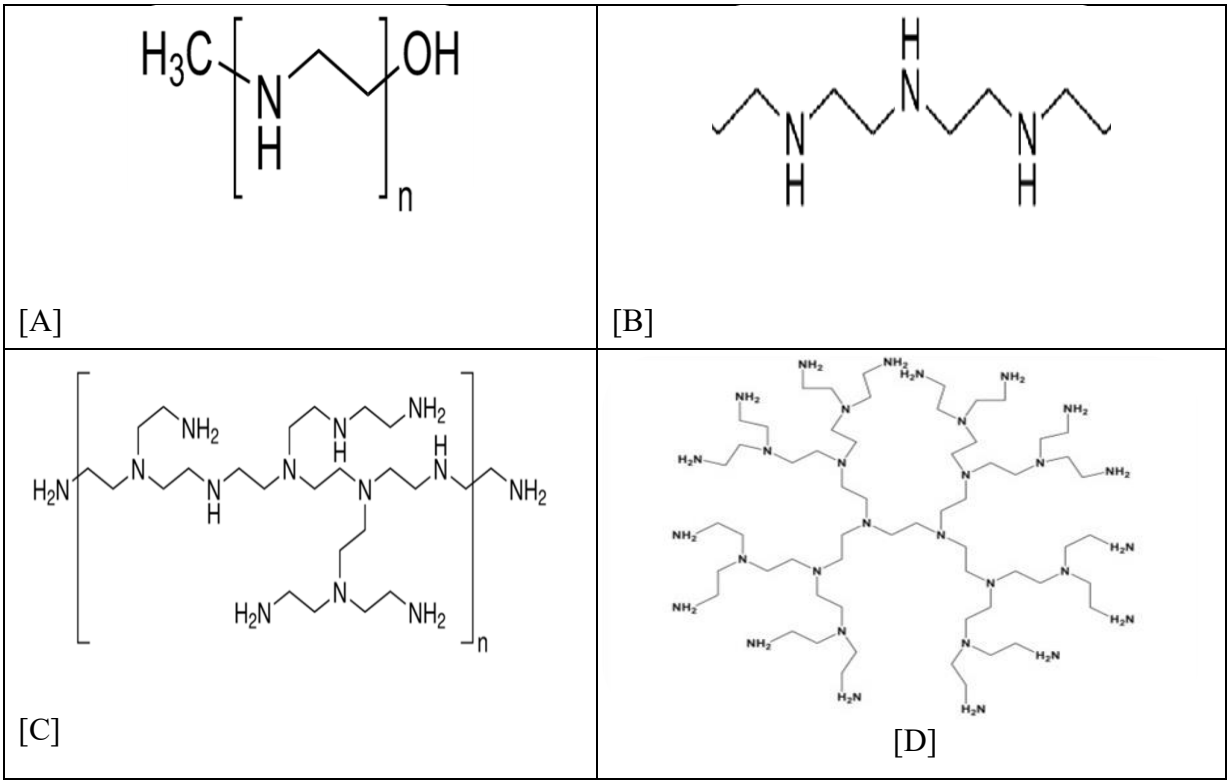
The polymers have an important role in the development of novel drug delivery system in recent years. In the field of gene and tissue engineering, polycationic polymers are extensively employed for the preparation of nanoparticles, microparticles, liposomes and polyplex. These polymers are macromolecules that consist of repeated units of positive charges [1]. Polyethylenimine (PEI) is considered as the ‘gold standard' when compared with other cationic polymers like polyamidoamine or chitosan for transgene expression [2]. It was introduced in the year 1930 [3]. PEI is a synthetic cationic polymer which contains two aliphatic carbons (CH2CH2) and amine groups [4]. The amine groups are present at different positions of the structure in branches, chain ends and backbone [3, 5]. The positive charged density is due to the presence of protonated amino nitrogen chain [6]. The third atom of the polymer has a protonated chain [7]. It has numerous applications in the field of medicine- target drug delivery system, drug carrier, genetic engineering and biomedical products. Branched PEI (BPEI) preparation was first patented in 1940 [8, 9]. Boussif et al. suggested the idea of complexing PEI with DNA for gene delivery in 1955 [10, 11]. PEI acts a prominent gene delivery vehicle and a carrier system [12]. PEI has been extensively employed as a co-

delivery agent in dosage forms and gene therapy owing to its high effectiveness and its low cost [7]. PEI is a polyfunctional aziridine that is chemically known as poly (imino (1,2-ethanediyl)) that is produced by the ring-opening polymerization of aziridines [7]. The synthetic polymer research has been rapidly developed, which made it more and more important in the contemporary field of drug delivery and gene therapy [13]. The mechanism of the cationic transfection system used by PEI is the high number of positive charges on its nitrogen atoms, which produces high-efficiency transfection efficiency both for DNA and RNA [14, 15]. It is expected that the global market growth of PEI would increase tremendously over 15% by 2030 to 474 million USD, which was 409 million USD in 2021 [3].

2. Structure and types

PEI comprises of ethylene units and secondary amine groups [16]. It is available in two structural arrangements: Linear PEI (LPEI) $(CH_2CH_2NH)_n$ and Branched PEI (BPEI) $H(NHCH_2CH_2)_nNH_2$ [7, 17]. Additionally, dendrimeric structural forms are offered as seen in figure 1. Branched PEI is made up of 25% of primary amine, 50% of secondary amine [6]. The hyperbranched PEI is synthesized by polymerizing the aziridine monomers. The nitrogen atoms present in each branch is between 3-35. This branched structure creates a spherical structure that encapsulates drug molecules and nanoparticles [16]. The high pKa value of PEI (shown in the A549 cells study) makes the PEI cytotoxic [15]. The presence of amines in PEI in adequate amounts can result in having various degree of modification and adaptability to efficiently deliver genes in gene therapy [2]. The linear PEI is prepared by the hydrolysis reaction [15] and post modification of the polymer poly(2-oxazolines). LPEI comprises of only secondary amines while BPEI has primary, secondary and tertiary amines [2]. The stability of the linear form is less than the branched PEI structure [15].

Figure 1: Structure of types of PEI



[A]- Polyethylenimine (PEI), [B] - Linear PEI (LPEI),

[C]- Branched PEI (BPEI), [D]- Dendrimeric PEI

2.1 Structural properties

The polymer chains are coiled at high pH level (basic medium) and get extended at low pH (acidic medium) [18]. The structure of PEI can be easily altered and tuned for increasing its biocompatibility and efficient drug delivery [19]. The low molecular weight PEI results in frequent cross linking between the biodegradable linker and results in consistently improved biocompatibility. Therefore, the preference is for PEI of high molecular weight (22-25kDa) [12, 2]. Polymer with high molecular weight results in highly efficient and non-biodegradable polymer [10]. The wide range of molecular weights of PEI are 700 Da, 2, 25, 50, 70, 800 kDa. The protonation effect of the amine group increases from around 20% at neutral pH to around 45% at a low pH of 5 [11].

3. Characterization of PEI

- Colour - Pale yellow liquid or colourless
- Odour - Smells like ammonia
- Consistency - Viscous
- Nature - Hygroscopic

Figure 2: Polyethylenimine

Table 1: Properties of PEI

Properties	Description
Melting point	59°C - 60°C
Boiling point	250°C
Density	1.030 g/mL at 25 °C
Vapor pressure	9 mmHg (20 °C)
Refractive index	n20/D 1.5290
Flash point	>230 °F
Storage temperature	2-8°C
Specific Gravity	1.045 (20/4°C)
pH	pH (50g/l, 25°C): 10～12

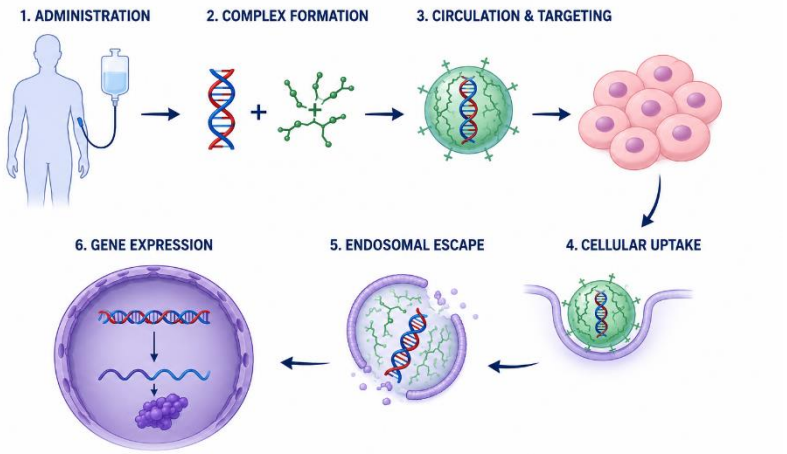
Viscosity	200-500 cP (25°C)

- Linear PEI – Semi crystalline solid
- Branched PEI – Amorphous polymer
- Melting point of LPEI is 67° C
- Solubility of LPEI - Soluble at low pH level, methanol, hot water, chloroform and is insoluble in acetone, benzene, cold water, ethyl ether
- BPEI – Soluble in water [20, 21, 22]

4. Principle of gene therapy delivery with PEI

PEI is one of the most effective non-viral vectors to transport DNA or RNA into the target cells in gene therapy. It has both high DNA condensation and membrane destabilizing property and complex with DNA to form polyplex. It prevents the degradation of the genetic material and improves its entry into the nucleus [38]. The abundant number of amine groups in the structure of PEI is proposed to account for its ability to buffer the endosome, the "proton-sponge" hypothesis. This buffering effect creates osmotic swelling, cell membrane rupture, and the polyplexes enter the cell. It inhibits the degradation in endosomal-lysosomal compartments. This mechanism has been demonstrated in the studies of chloride entry and endosomal disruption in cells. The electrostatic interaction that takes place between the positively charged complex of PEI and the negatively charged cell membrane is responsible. [39] The main mechanism involved in the internalization of non-viral vectors (PEI) into the cells is endocytosis, where the cells uptake molecules from vesicles. Depending on cell type and PEI morphology, endocytosis is mediated by the clathrin-mediated endocytosis, caveolae-mediated endocytosis and macropynocytosis. [39]

Figure 3: Principle of gene delivery using PEI



5. Applications of Polyethylenimine for Parkinsonism

5.1 Polyethylenimine in Gene Therapy

Vascular endothelial growth factor (VEGF) is employed in therapeutic treatment of Parkinson's disease in gene therapy. A combination of polylysine-modified polyethylenimine (PEI-PLL) was used to incorporate VEGF gene to determine its efficacy. This non-viral gene carrier study was performed in animals and in

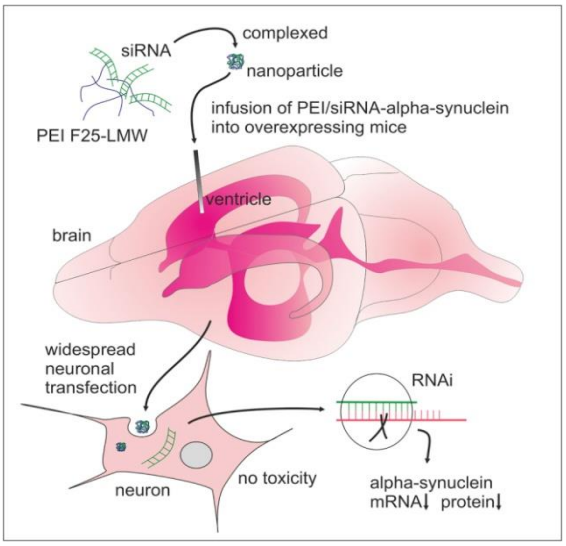
cell culture. VEGF is a neuroprotective agent that blocks neurotoxic activity by 6-hydroxydopamine (6-OHDA) which has been reported in behavioural analyses. It protects the dopaminergic (DA) cell bodies in the Substantia Nigra Pars Compacta (SNPc) and preserved their nerve terminals in the striatum. The VEGFR delivery vehicle composed of combination carrier PEI-PLL inhibited the apoptotic process and decreased the neuroinflammation resulting from microglial activation. Most dopaminergic neurons can be identified in immunostaining by their expression of the standard enzyme marker tyrosine hydroxylase (TH). These experimental procedures were conducted in the Parkinson's models rats. This study will bring about evolution development in Parkinsonism gene therapy [23].

5.2 Nanoparticle in ICV injection

Patients with Parkinson's have a protein (SNCA or alpha-synuclein) that clumps and misfolds in the brain. Imbalance of storage results in neurodegenerative disorders. This protein is silenced so as no toxic build up occurs. siRNA normally has difficulty in entering neurons and the survival period is shorter. The scientists took a polymer called PEI F25-LMW, which is positively charged, and made a particle complex with the negatively charged siRNA molecules. Small interfering RNA (siRNA) is encapsulated in PEI nanoparticles, which help to protect siRNA from degradation and promote its internalization into target cells with accurate delivery to the cytoplasm. siRNA can be highly delivered into the brain and into neurons by using PEI-mediated delivery. siRNAs are short pieces of RNA which are capable of binding to and degrading the mRNA of the SNCA gene. This is to lower human SNCA mRNA levels [24]. Another major advantage of lipid-conjugation of bPEI is the increase in siRNA delivery [25].

Thy1-aSyn mice were used for the experiments in which human wild-type α-synuclein was overexpressed in the brain. A single injection dose of 0.75 µg PEI/siRNA was injected into the mice. Intracerebroventricular (ICV) injection involves the administration of therapeutic complexes directly into the fluid-filled chambers of the brain (lateral ventricles), which helps them cross the blood-brain barrier. It is widespread in CNS and gets to the region of the lumbar spinal cord. 5 days after administration, SNCA mRNA in the striatum was decreased to 65% and SNCA protein decreased to 50%. There was no adverse reaction reported. PEI has been engineered to target specific tissue in the brain and neuronal cells [24]

Figure 4: Nanoparticle complex delivery to brain



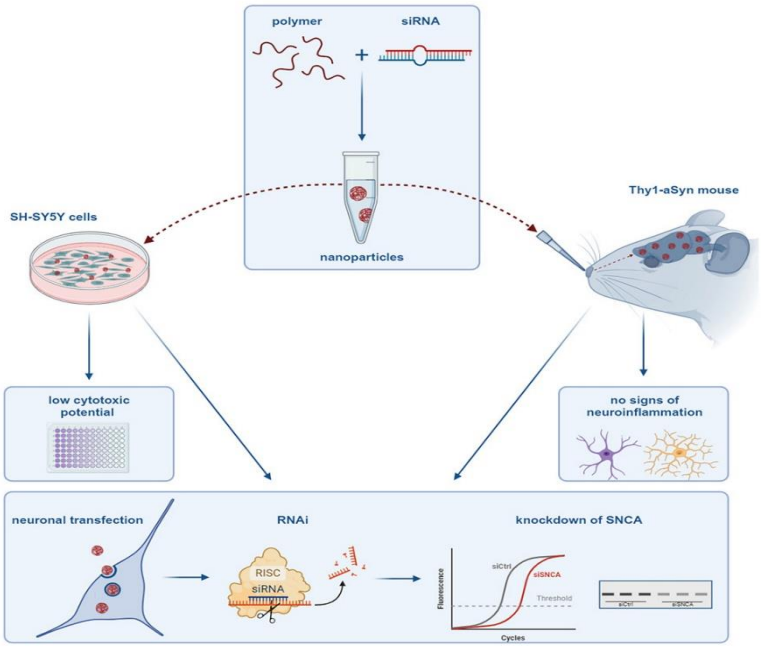
5.3 Nasal spray gene therapy

The mouse model for Parkinson's disease (PD) was treated by nasal spray gene therapy and illustrated in figure 4. It is a nose-to-brain delivery which penetrates the blood-brain barrier (BBB) directly into the brain. It provides the genetic information (siRNA) to the target gene (SNCA) and prevents the accumulation of the alpha-synuclein (aSyn) protein. Unmodified PEI F25 and tyrosine-modified branched and linear PEI (P10Y and LP10Y) were used for carrying and protecting the genetic materials. Tyrosine modification will help with stability, uptake and transfection efficiency, and biocompatibility. Its usefulness is strongly related to the intrinsic properties of the polymer PEI including its molecular weight and structural architecture [26].

Intranasal delivery resulted in PEI/ polypropylenimine-siRNA nanoparticle formulations reaching the brain and being widely distributed throughout multiple regions such as the olfactory bulb, substantia nigra and prefrontal cortex. These experimental procedures are indicative of the ability of intranasal PEI/PPI based nanocarriers to deliver therapeutic siRNA to the brain [26]. Pharmacokinetic studies have been reported of more efficient delivery of siRNA-loaded nanosized micelles to the brain than to the bloodstream when administered intravenously in rats [26]. The advantage of nasal spray gene therapy is that the onset of action is rapid and is suitable for self-administration. It also resists the first pass metabolism and improves bioavailability [27].

Complex PEI/PPI–siRNAs nanoparticles showed good biocompatibility and ability to significantly decreased the mRNA expression of SNCA in aSyn-overexpressing SH-SY5Y neuroblastoma cells. Intranasal injection led to widespread distribution of PEI/PPI-based nanoparticles throughout the brain and efficient uptake by dopaminergic neurons of the substantia nigra pars compacta (SNc) in Thy1-aSyn mice. PEI/PPI-based nanocarriers delivered siRNA intranasally to the mouse model and led to the reduction of the SNCA mRNA and proteins levels. This treatment did not cause neuroinflammation [26].

Figure 4: Intranasal administration of PEI based nanoparticles



6. Limitations and challenges of PEI

Although the formulations based on PEI are beneficial and potent, their biocompatibility is still a challenge [28]. It does not have a definite 3D structure and a small number of clinical trials have been performed [29]. To make PEI biocompatible, some strategies are employed including increasing the charge density, molecular weight, branching structure, and adding chemically compatible modifications to the PEI. Existing strategies which aim to improve the safety of their security are explored, in regard of recent developments and future considerations. This promotes the translation of the delivery systems based on PEI into clinical applications of genes, drugs and vaccines [28, 30].

PEI polyplexes do not have a long circulation time in the blood, and therefore are not particularly stable in the circulation. Though effective results have been obtained from preclinical animal studies model, clinical trials are limited due to safety concerns [2, 19]. However, its use as treatments in the clinic has been inhibited by its cytotoxic effect [31]. The toxicity is primarily linked to the low biodegradability and the high positive charge density of PEI, which can cause disruptions in cell membranes, oxidative stress, and affect mitochondrial function. The low-molecular-weight compounds of PEI are less toxic to cells than the high molecular weight PEI. However, there are some adverse effects which can be mitigated with chemical modification, for example, PEGylation. The other techniques involve chemical derivatisation, and nanoparticle neutralisation and surface shielding, which have shown the greatest potential to reduce the toxicity of PEI polymers [28].

PEI can be chemically modified so that it can be targeted. There are two strategies to increase the transfection efficiency of LMW-PEI, known as “PEI dilemma” [19, 32, 33]. LPEI is crosslinked with bioreducible links, like carbamates, esters and disulphide linkages, which provide biodegradable polymers with the properties of high molecular weight PEI with high transfection [19, 34]. It also offers adequate levels of positive charges and lowers the toxicity. pH sensitive linkers such as polyaspartate and hydrazone were also used [19, 35]. Modification of PEI via the introduction of polysaccharides and hydrophobic groups is another way to enhance biocompatibility of PEI [19, 36].

7. Future aspects

In 2025, the global polyethyleneimine (PEI) market value was estimated at USD 454.11 million and is expected to touch USD 517.36 million by 2035, at a compound annual growth rate (CAGR) of 1.33% for the forecast period of 2026 to 2035. With the biomedical research and pharmaceutical applications, the use of PEI is expected to continue to grow, helping to advance the market further, and the latest advancements in polymer chemistry and manufacturing technologies is also anticipated to further accelerate the market growth of PEI [37]. Initiatives for investigating toxicity associated with PEI and for finding effective ways to minimize the effects of the toxicity are required. It results in the development of PEI delivery system towards future clinical applications [28].

8. Key takeaways

Polyethylenimine (PEI) has become a leading and very prominent material to the contemporary world of advanced therapeutics, especially in the fast-developing areas of targeted drug and gene delivery. With ongoing progress in biomaterials engineering, a growing number of studies are focusing on the exact design, chemical synthesis, and clinical use of complex and sophisticated, PEI-based delivery architectures [28]. It is readily engineered and adapted to develop an extensive range of nanosized and engineered

carriers such as thin macromolecular films, cross-linked hydrogels, as well as other customized delivery matrices. This structural versatility makes PEI based systems ideal to meet a wide range of rigid biomedical needs, accommodating a variety of routes of clinical administration and efficient in transcellular delivery of therapeutic payloads in a safe manner to target cells [19].

9. Conflict of interest

The authors declare that there is no conflict of interest with this review article.

10. Acknowledgement

The authors would like express their sincere gratitude to the institution and all individuals for their support and assistance during the preparation of this review article.

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